

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 September 2005 (15.09.2005)

PCT

(10) International Publication Number
WO 2005/085203 A1

(51) International Patent Classification⁷: C07D 221/12,
A61K 31/473

(21) International Application Number:
PCT/EP2005/051022

(22) International Filing Date: 8 March 2005 (08.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04100989.5 10 March 2004 (10.03.2004) EP
05100539.5 27 January 2005 (27.01.2005) EP

(71) Applicant (for all designated States except US): ALTANA
PHARMA AG [DE/DE]; Byk-Gulden-Str. 2, 78467 Kon-
stanz (DE).

(72) Inventors (for all designated States except CA, PH, US):
SCHMIDT, Beate; Allensbacher Str. 5, 78476 Allens-
bach (DE). FLOCKERZI, Dieter; Ackerweg 26, 78476
Allensbach (DE). HATZELMANN, Armin; Alter Wall 3,
78467 Konstanz (DE). ZITT, Christof; Mainaustr. 209 D,
78464 Konstanz (DE). BARSIG, Johannes; Bleichenweg
11, 78467 Konstanz (DE). MARX, Degenhard; Obere
Reute 15, 78345 Moos (DE). KLEY, Hans-Peter; Im
Weinberg 3b, 78476 Allensbach (DE).

(72) Inventor; and

(75) Inventor/Applicant (for US only): KAUTZ, Ulrich
[DE/DE]; Prof.-Schmider-Str. 12, 78476 Allensbach (DE).

(74) Agents: WILD, Robert et al.; c/o ALTANA Pharma AG,
Byk-Gulden-Str. 2, 78467 Konstanz (DE).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
ZM, ZW.

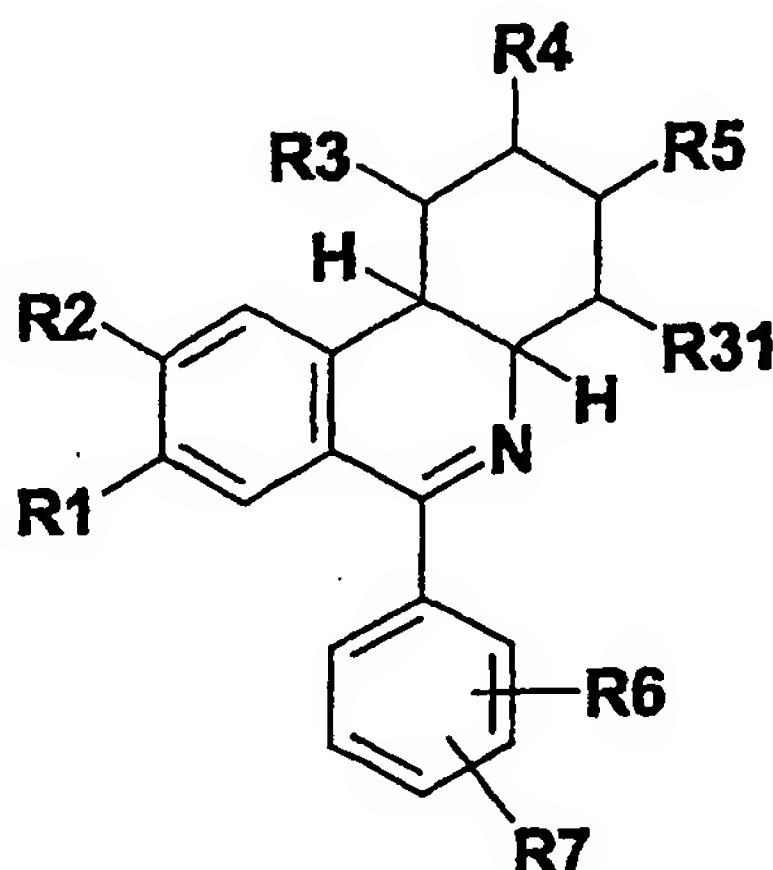
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,
EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA,
ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ,
NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT,
BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR,
HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG)

[Continued on next page]

(54) Title: NOVEL DIFLUOROETHOXY-SUBSTITUTED HYDROXY-6-PHENYLPHENANTHRIDINES AND THEIR USE
AS PDE4 INHIBITORS



(I)

(57) Abstract: Compounds of a certain formula (I), in which R1, R2,
R3, R31, R4, R5, R6 and R7 have the meanings indicated in the de-
scription, are novel effective PDE4 inhibitors.

WO 2005/085203 A1



— of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

NOVEL DIFLUOROETHOXY-SUBSTITUTED HYDROXY-6-PHENYLPHENANTHRIDINES AND THEIR USE
AS PDE4 INHIBITORS

Field of application of the invention

The invention relates to novel difluoroethoxy-substituted hydroxy-6-phenylphenanthridine derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

Known technical background

The International Patent applications WO99/57118 and WO02/05616 describe 6-phenylphenanthridines as PDE4 inhibitors.

In the International Patent application WO99/05112 substituted 6-alkylphenanthridines are described as bronchial therapeutics.

In the European Patent application EP 0490823 dihydroisoquinoline derivatives are described which are useful in the treatment of asthma.

In the International Patent application WO97/35854 phenanthridines substituted in the 6-position are described as bronchial therapeutics.

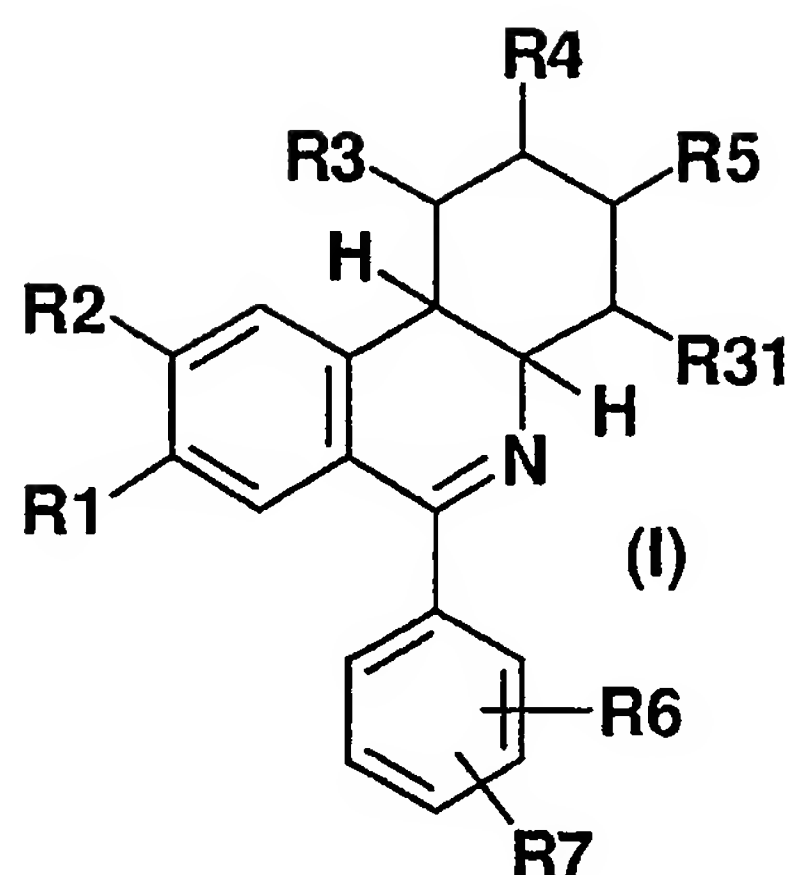
The International Patent applications WO2004/019944 and WO2004/019945 disclose hydroxy-substituted 6-phenylphenanthridines as PDE4 inhibitors.

Description of the invention

It has now been found that the novel difluoroethoxy-substituted 2- or 3-hydroxy-6-phenylphenanthridines described in greater detail below differ from the previously known compounds by unanticipated and sophisticated structural alterations and have surprising and particularly advantageous properties.

The invention thus relates to compounds of formula I,

- 2 -



in which

either, in a first aspect (aspect 1) according to the present invention,

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-4C-alkoxy, and

R2 is 2,2-difluoroethoxy,

or, in a second aspect (aspect 2) according to the present invention,

R1 is 2,2-difluoroethoxy, and

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R3 is hydrogen or 1-4C-alkyl,

R31 is hydrogen or 1-4C-alkyl,

either, in a first embodiment (embodiment a) according to the present invention,

R4 is -O-R41, in which

R41 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-7C-alkylcarbonyl, or completely or predominantly fluorine-substituted 1-4C-alkyl, and

R5 is hydrogen or 1-4C-alkyl,

or, in a second embodiment (embodiment b) according to the present invention,

R4 is hydrogen or 1-4C-alkyl, and

R5 is -O-R51, in which

R51 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-7C-alkylcarbonyl, or completely or predominantly fluorine-substituted 1-4C-alkyl,

R6 is hydrogen, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, halogen, nitro, cyano, hydroxyl, 1-4C-

- 3 -

alkylcarbonyloxy, amino, mono- or di-1-4C-alkylamino, phenyl, phenyl-1-4C-alkyl, 1-4C-alkyl-carbonylamino, phenoxy, 1-4C-alkylcarbonyl, or C(O)OR₆₁, wherein

R₆₁ is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R₇ is hydrogen, 1-4C-alkyl, hydroxyl, halogen, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or C(O)OR₆₁,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

1-7C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 7 carbon atoms. Examples which may be mentioned are the heptyl, isoheptyl (5-methylhexyl), hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethylbutyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl or methyl radicals.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

3-7C-Cycloalkoxy represents cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkylmethoxy represents cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

As completely or predominantly fluorine-substituted 1-4C-alkoxy, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy radicals may be mentioned. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy radicals are replaced by fluorine atoms.

As completely or predominantly fluorine-substituted 1-4C-alkyl, for example, the 2,2,3,3,3-pentafluoropropyl, the perfluoroethyl, the 1,2,2-trifluoroethyl, in particular the 1,1,2,2-tetrafluoroethyl, the 2,2,2-trifluoroethyl, the trifluoromethyl and particularly the difluoromethyl radicals may be mentioned. "Predomi-

nantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkyl radicals are replaced by fluorine atoms.

1-2C-Alkylenedioxy represents, for example, the methylenedioxy $[-O-CH_2-O-]$ and the ethylenedioxy $[-O-CH_2-CH_2-O-]$ radicals.

1-4C-Alkoxy-1-4C-alkyl represents one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxy-methyl, the methoxyethyl and the isopropoxyethyl radicals, particularly the 2-methoxyethyl and the 2-isopropoxyethyl radicals.

1-4C-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkyl radicals. An example which may be mentioned is the acetyl radical.

1-7C-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-7C-alkyl radicals. Examples which may be mentioned are the acetyl, propionyl, butanoyl and hexanoyl radicals.

Hydroxy-2-4C-alkyl represents 2-4C-alkyl radicals, which are substituted by a hydroxyl group. Examples which may be mentioned are the 2-hydroxyethyl and the 3-hydroxypropyl radicals.

In addition to the nitrogen atom, mono- or di-1-4C-alkylamino radicals contain one or two of the abovementioned 1-4C-alkyl radicals. Di-1-4C-alkylamino is preferred and here, in particular, dimethyl-, diethyl- or diisopropylamino.

Halogen within the meaning of the invention is bromine, chlorine or fluorine.

3-7C-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkylmethyl represents a methyl radical which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Preferably, the 3-5C-cycloalkylmethyl radicals cyclopropylmethyl, cyclobutylmethyl and cyclopentylmethyl may be mentioned.

Phenyl-1-4C-alkyl represents one of the abovementioned, phenyl-substituted 1-4C-alkyl radicals. Examples which may be mentioned are the phenethyl and the benzyl radicals.

1-4C-Alkylcarbonyloxy represents a carbonyloxy group to which one of the abovementioned 1-4C-alkyl radicals is bonded. An example which may be mentioned is the acetoxy radical $[\text{CH}_3\text{C}(\text{O})-\text{O}-]$.

1-4C-Alkylcarbonylamino represents an amino radical which is substituted by one of the abovementioned 1-4C-alkylcarbonyl radicals. An example which may be mentioned is the acetamido radical $[\text{CH}_3\text{C}(\text{O})-\text{NH}-]$.

Exemplary phenyl radicals substituted by R6 and R7 which may be mentioned are the radicals 4-acetamidophenyl, 3-acetamidophenyl, 4-acetoxyphenyl, 3-aminophenyl, 4-aminophenyl, 2-bromophenyl, 4-bromophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2-chloro-4-nitrophenyl, 4-diethylamino-2-methylphenyl, 4-methoxyphenyl, 3-methoxyphenyl, 2-chloro-5-nitrophenyl, 4-chloro-3-nitrophenyl, 2,6-dichlorophenyl, 3,5-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dibromophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-diethylaminophenyl, 4-dimethylaminophenyl, 2-fluorophenyl, 4-fluorophenyl, 3-fluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 2-chloro-6-fluorophenyl, 2-fluoro-5-nitrophenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 3,4-dichlorophenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 2-hydroxy-4-methoxyphenyl, 2,4-dihydroxyphenyl, 2-methoxyphenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,4-dimethoxyphenyl, 3-dimethylaminophenyl, 2-dimethylaminophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-chloro-6-methylphenyl, 4-methyl-3-nitrophenyl, 2,4-dimethylphenyl, 2,6-dimethylphenyl, 2,3-dimethylphenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 4-ethoxyphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-benzylphenyl, 4-biphenyl, 4-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 3-cyclopentyloxyphenyl, 4-cyclopentyloxyphenyl, 4-cyclohexyloxyphenyl, 3-cyclohexyloxyphenyl, 3-cyclopropylmethoxyphenyl, 4-cyclopropylmethoxyphenyl, 3-cyclopropylmethoxy-4-methoxyphenyl, 3-cyclopropylmethoxy-4-difluoromethoxyphenyl, 3-cyclopropylmethoxy-4-ethoxyphenyl, 4-cyclopropylmethoxy-3-methoxyphenyl, 3-cyclopropylmethoxy-5-methoxyphenyl, bis-3,4-cyclopropylmethoxyphenyl, bis-3,5-cyclopropylmethoxyphenyl, 3,4-dicyclopentyloxyphenyl, 3-cyclopentyloxy-4-methoxyphenyl, 4-cyclopentyloxy-3-methoxyphenyl, 3-cyclopropylmethoxy-4-cyclopentyloxyphenyl, 3-cyclopentyloxy-5-methoxyphenyl, 4-cyclopropylmethoxy-3-cyclopentyloxyphenyl, 3-cyclobutyloxy-4-methoxyphenyl, 3-cyclopropylmethoxy-4-acetylaminophenyl, 4-carboxyphenyl, 4-methoxycarbonylphenyl, 4-ethoxycarbonylphenyl, 4-isopropoxycarbonylphenyl, 3-carboxyphenyl, 3-methoxycarbonylphenyl, 3-ethoxycarbonylphenyl, 3-isopropoxycarbonylphenyl, 4-methoxycarbonyl-3-methylphenyl, 3-chloro-4-methoxycarbonylphenyl, 3-bromo-4-methoxycarbonylphenyl, 3-fluoro-4-methoxycarbonylphenyl, 3-hydroxy-4-methoxycarbonylphenyl, 2-chloro-4-methoxycarbonylphenyl, 2-bromo-4-methoxycarbonylphenyl, 2-fluoro-4-methoxycarbonylphenyl, 2-methoxy-4-methoxycarbonylphenyl, 4-methoxycarbonyl-2-methylcarbonylphenyl, 4-fluoro-3-methoxycarbonylphenyl, 4-ethoxy-3-methoxycarbonylphenyl, 4-methoxy-3-methoxycarbonylphenyl, 4-isopropoxy-3-methoxycarbonylphenyl, 3-methoxycarbonyl-4-methylphenyl, 5-tert-butyl-3-methoxycarbonylphenyl, 3-methoxycarbonyl-5-methylphenyl, 3-bromo-5-methoxy-

carbonylphenyl, 3-chloro-5-methoxycarbonylphenyl, 3-methoxy-5-methoxycarbonylphenyl, 3-acetoxy-4-methoxycarbonylphenyl, 4-methoxycarbonyl-2-nitrophenyl, 4-methoxycarbonyl-2-phenylphenyl, 2-cyano-4-methoxycarbonylphenyl, 4-acetoxy-3-methoxycarbonylphenyl, 3-methoxycarbonyl-4-nitrophenyl, 3-methoxycarbonyl-5-phenylphenyl, 5-cyano-3-methoxycarbonylphenyl, 5-methoxycarbonyl-3-nitrophenyl, 4-methoxy-3-propoxy-phenyl, 4-butoxyphenyl, 4-difluoromethoxyphenyl, 3-difluoromethoxy-phenyl, 3,4-bis-difluoromethoxyphenyl, 4-(1,1,2,2-tetrafluoroethoxy)-phenyl, 3-fluoro-4-methoxyphenyl or 4-phenoxyphenyl.

As it is known for the person skilled in the art, compounds comprising nitrogen atoms can form N-oxides. Particularly, imine nitrogen, especially heterocyclic or heteroaromatic imine nitrogen, or pyridine-type nitrogen ($=N$ -) atoms, can be N-oxidized to form the N-oxides comprising the group $=N^+(O^-)$. Thus, the compounds according to the present invention comprising the imine nitrogen atom in position 5 of the phenylphenanthridine backbone and, optionally (depending on the meaning of the substituents), one or more further nitrogen atoms suitable to exist in the N-oxide state ($=N^+(O^-)$) may be capable to form (depending on the number of nitrogen atoms suitable to form stabile N-oxides) mono-N-oxides, bis-N-oxides or multi-N-oxides, or mixtures thereof.

The term N-oxide(s) as used in this invention therefore encompasses all possible, and in particular all stabile, N-oxide forms, such as mono-N-oxides, bis-N-oxides or multi-N-oxides, or mixtures thereof in any mixing ratio.

Possible salts for compounds of the formula I -depending on substitution- are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, it being possible to employ the acids in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or calcium, aluminum, magnesium, titanium, ammonium, meglumine or guanidinium salts, where here too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

- 7 -

Pharmacologically intolerable salts which can initially be obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts, when they are isolated, for example, in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula I, and also all solvates and in particular all hydrates of the salts of the compounds of the formula I.

The substituents R6 and R7 of compounds of formula I can be attached in the ortho, meta or para position with respect to the binding position in which the 6-phenyl ring is bonded to the phenanthridine ring system, whereby preference is given to the attachment in the meta or in the para position. In another embodiment, R7 is hydrogen, and R6 is bonded to the meta or para position.

Compounds of formula I more worthy to be mentioned are those in which

either, in a first aspect (aspect 1) according to the present invention,

R1 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy, and

R2 is 2,2-difluoroethoxy,

or, in a second aspect (aspect 2) according to the present invention,

R1 is 2,2-difluoroethoxy, and

R2 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

either, in a first embodiment (embodiment a) according to the present invention,

R4 is -O-R41, in which

R41 is hydrogen or 1-4C-alkylcarbonyl, and

R5 is hydrogen,

or, in a second embodiment (embodiment b) according to the present invention,

R4 is hydrogen, and

R5 is -O-R51, in which

R51 is hydrogen or 1-4C-alkylcarbonyl,

- 8 -

R6 is 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 3-7C-cycloalkylmethoxy, halogen, nitro, cyano, hydroxyl, 1-4C-alkylcarbonyloxy, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, phenoxy or C(O)OR₆₁, wherein
R₆₁ is hydrogen or 1-4C-alkyl,
R7 is hydrogen, halogen, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, or 3-7C-cycloalkylmethoxy,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of formula I in particular worthy to be mentioned are those in which either, in a first aspect (aspect 1) according to the present invention,

R1 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy, and
R2 is 2,2-difluoroethoxy,
or, in a second aspect (aspect 2) according to the present invention,
R1 is 2,2-difluoroethoxy, and
R2 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,
R3 is hydrogen,
R₃₁ is hydrogen,
R4 is -O-R₄₁, in which
R₄₁ is hydrogen or 1-4C-alkylcarbonyl,
R5 is hydrogen,
R6 is 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 3-7C-cycloalkylmethoxy, halogen, nitro, cyano, hydroxyl, 1-4C-alkylcarbonyloxy, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, phenoxy or C(O)OR₆₁, wherein
R₆₁ is hydrogen or 1-4C-alkyl,
R7 is hydrogen, halogen, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, or 3-7C-cycloalkylmethoxy,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of formula I in more particular worthy to be mentioned are those in which either, in a first aspect (aspect 1) according to the present invention,

R1 is 1-2C-alkoxy, and
R2 is 2,2-difluoroethoxy,
or, in a second aspect (aspect 2) according to the present invention,
R1 is 2,2-difluoroethoxy, and
R2 is 1-2C-alkoxy,
R3 is hydrogen,

- 9 -

R31 is hydrogen,
R4 is -O-R41, in which
R41 is hydrogen,
R5 is hydrogen,
R6 is halogen, in detail fluorine,
R7 is halogen, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 3-7C-cycloalkylmethoxy, or, particularly, hydrogen,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Yet compounds of formula I in more particular worthy to be mentioned are those in which

R1 is 1-2C-alkoxy,
R2 is 2,2-difluoroethoxy,
R3 is hydrogen,
R31 is hydrogen,
R4 is -O-R41, in which
R41 is hydrogen,
R5 is hydrogen,
R6 is cyano, or halogen such as e.g. fluorine,
R7 is hydrogen,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

A special interest in the compounds according to this invention relates to those compounds which are included by one or, when possible, by more of the following embodiments:

A special embodiment of the compounds of the present invention include those compounds of formula I, in which R1 is 1-2C-alkoxy and R2 is 2,2-difluoroethoxy.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is 1-2C-alkoxy and R2 is 2,2-difluoroethoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, and R3 and R31 are both hydrogen.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R7 is hydrogen.

- 10 -

Another special embodiment of the compounds of the present invention include those compounds of formula I, in which R5 or, particularly, R4 is the radical (1-4C-alkylcarbonyl)-O- such as e.g. acetoxy, or hydroxyl, and all the other substituents are as defined in any compound which is said to be mentioned above.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R5 or, particularly, R4 is hydroxyl.

A preferred embodiment according to the present invention is aspect 1.

A further preferred embodiment according to the present invention is embodiment a.

A further preferred embodiment of the compounds of the present invention include compounds according to embodiment a, in which R5 and R41 are both hydrogen, and in which R1 is 1-2C-alkoxy and R2 is 2,2-difluoroethoxy, and R3 and R31 are hydrogen.

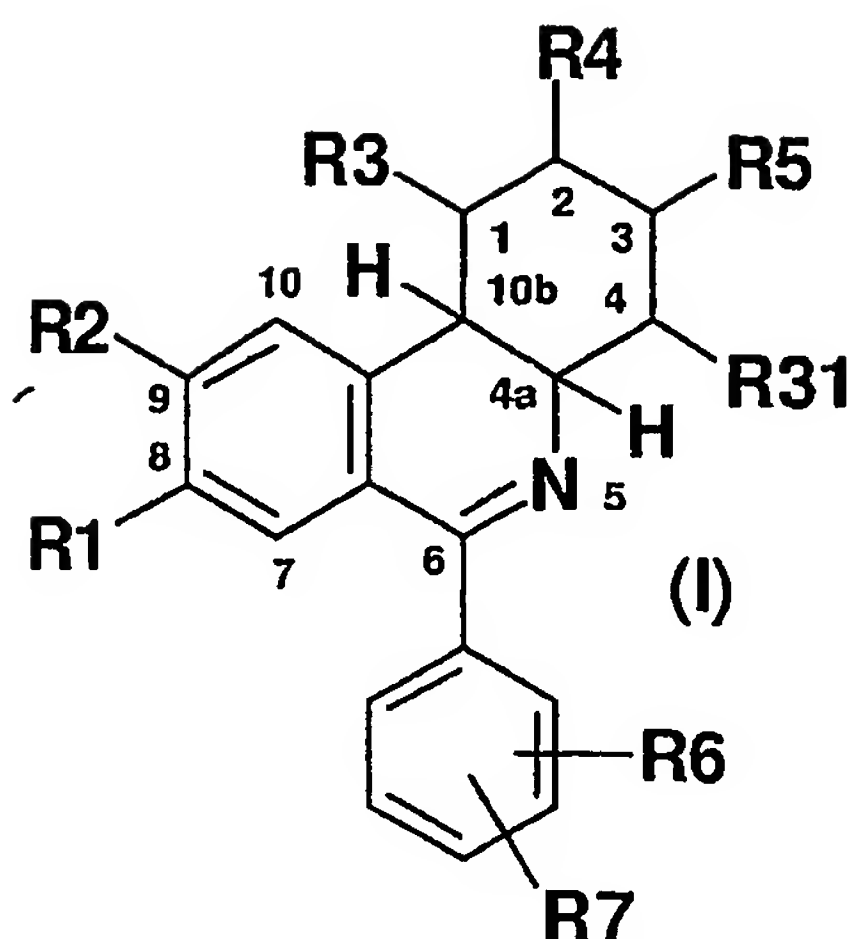
A yet further preferred embodiment of the compounds of the present invention include compounds according to embodiment a, in which R5 and R41 are both hydrogen, and in which R1 is methoxy and R2 is 2,2-difluoroethoxy, and R3 and R31 are hydrogen.

Suitable compounds according to the present invention more worthy to be mentioned include those compounds of formula I, in which R5 or, particularly, R4 is hydroxyl.

The compounds of formula I are chiral compounds having chiral centers at least in positions 4a and 10b and depending on the meanings of R3, R31, R4 and R5 additional chiral centers in positions 1, 2, 3 and 4.

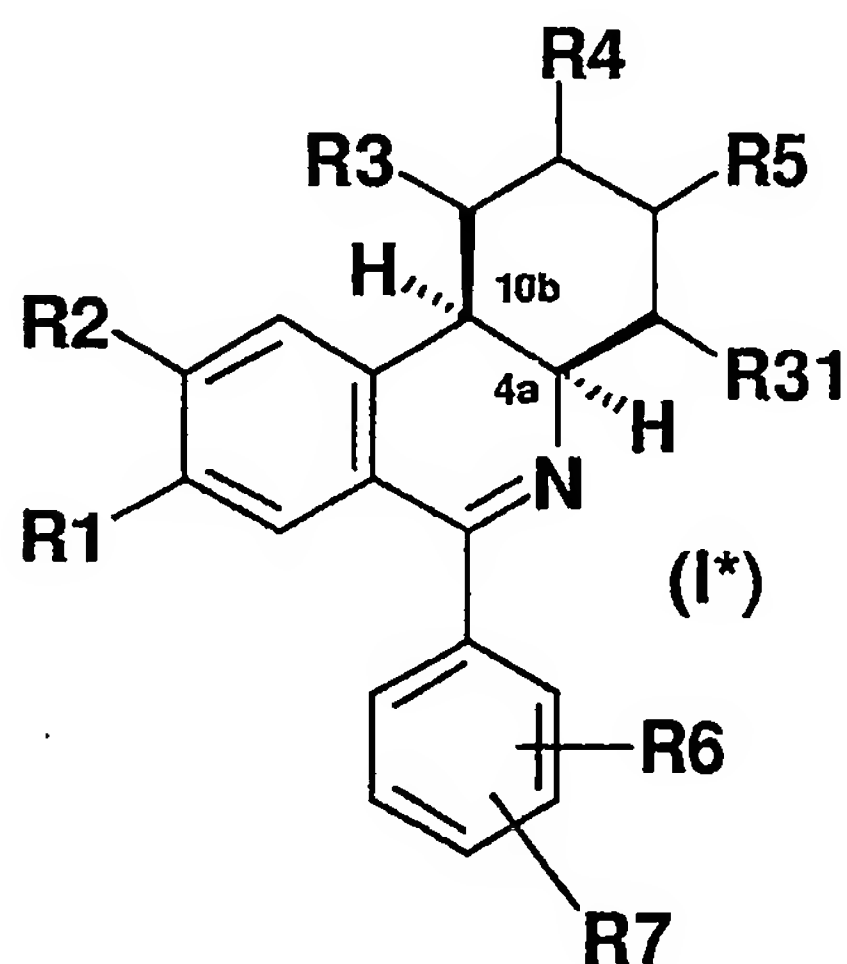
- 11 -

Numbering



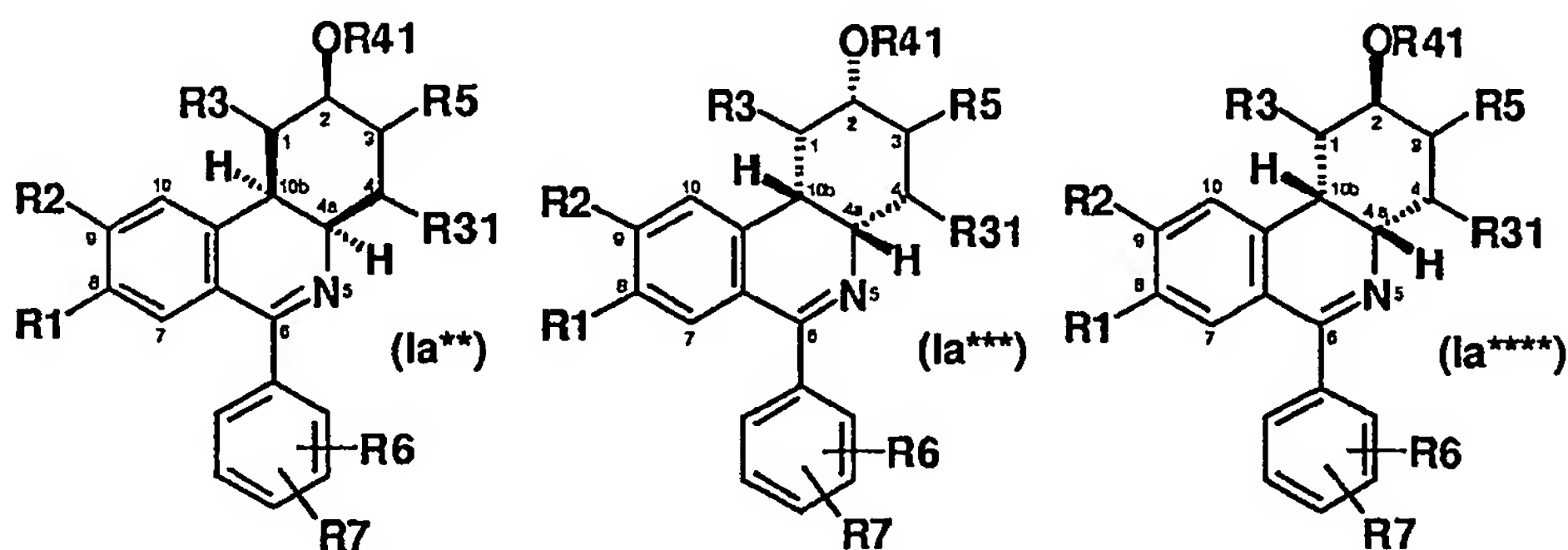
The invention includes all conceivable stereoisomers in pure form as well as in any mixing ratio. Preference is given to compounds of formula I in which the hydrogen atoms in positions 4a and 10b are in the cis position relative to one another. The pure cis enantiomers and their mixtures in any mixing ratio and including the racemates are more preferred in this context.

Particularly preferred in this context are those compounds of formula 1, which have with respect to the positions 4a and 10b the configuration shown in formula (I*):



If, for example, in compounds of formula I* R3, R31 and R5 have the meaning hydrogen and R4 has the meaning -OR41, then the configuration – according to the rules of Cahn, Ingold and Prelog – is R in the 4a position and R in the 10b position.

Further preferred compounds of the formula I according to embodiment a are those which have, with respect to the positions 2, 4a and 10b, the same configuration as shown in the formulae la** and la*** and la****:

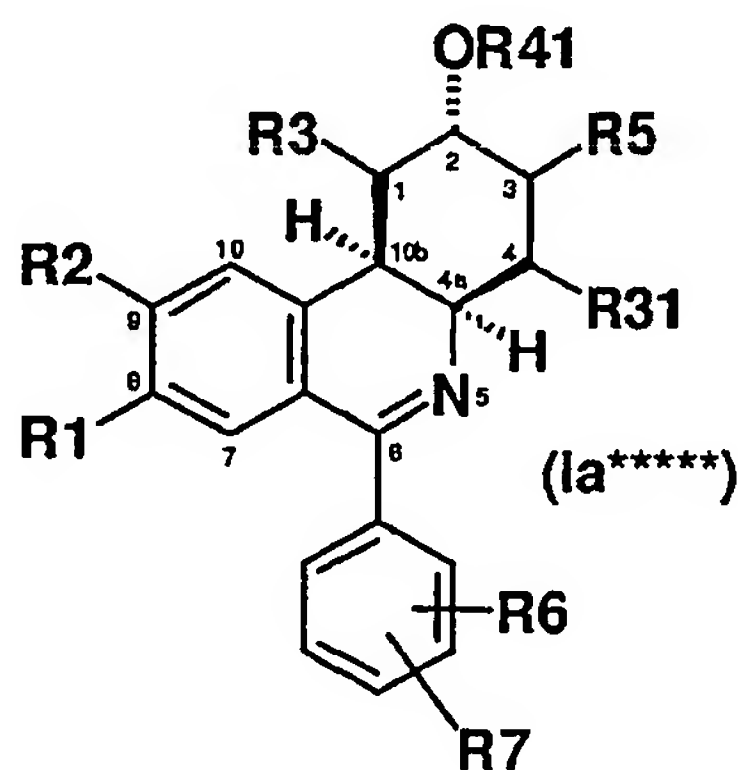


If, for example in compounds of the formula la** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is S in the position 2, R in the position 4a and R in the position 10b.

If, for example in compounds of the formula la*** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is R in the position 2, S in the position 4a and S in the position 10b.

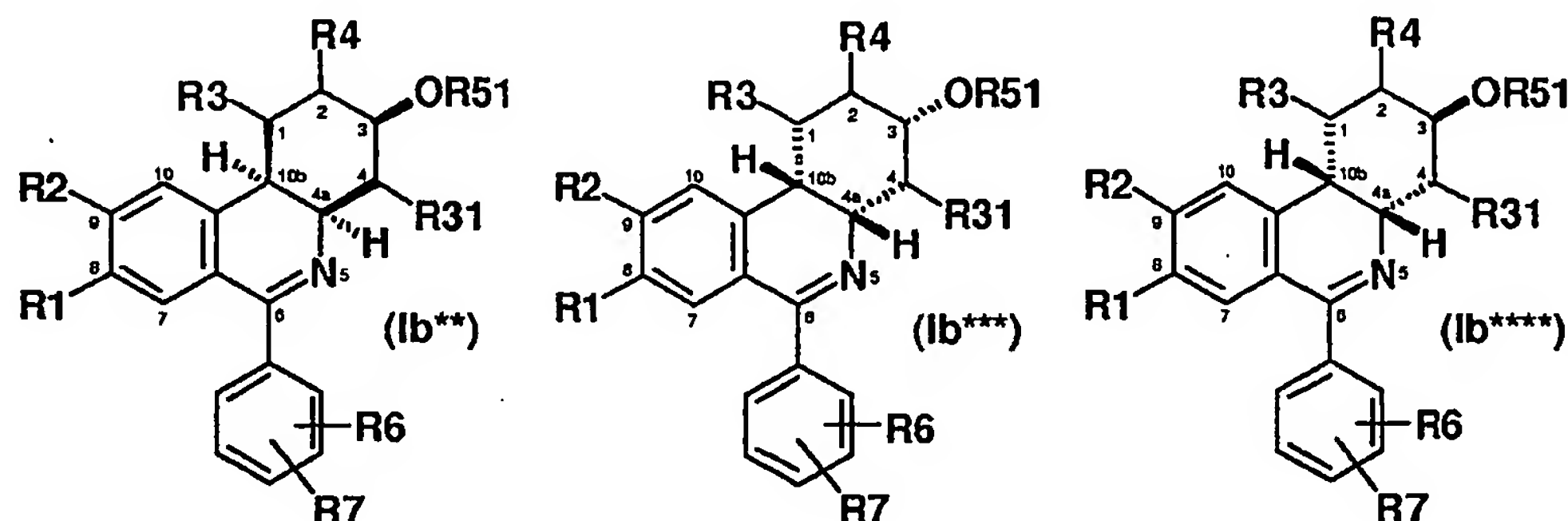
If, for example in compounds of the formula la**** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is S in the position 2, S in the position 4a and S in the position 10b.

In more particular preferred compounds of the formula I according embodiment a are those which have, with respect to the positions 2, 4a and 10b, the same configuration as shown in the formula la*****:



If, for example in compounds of the formula Ia**** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is R in the position 2, R in the position 4a and R in the position 10b.

Preferred compounds of the formula I according to embodiment b are those which have, with respect to the positions 3, 4a and 10b, the same configuration as shown in the formulae Ib** and Ib*** and Ib****:



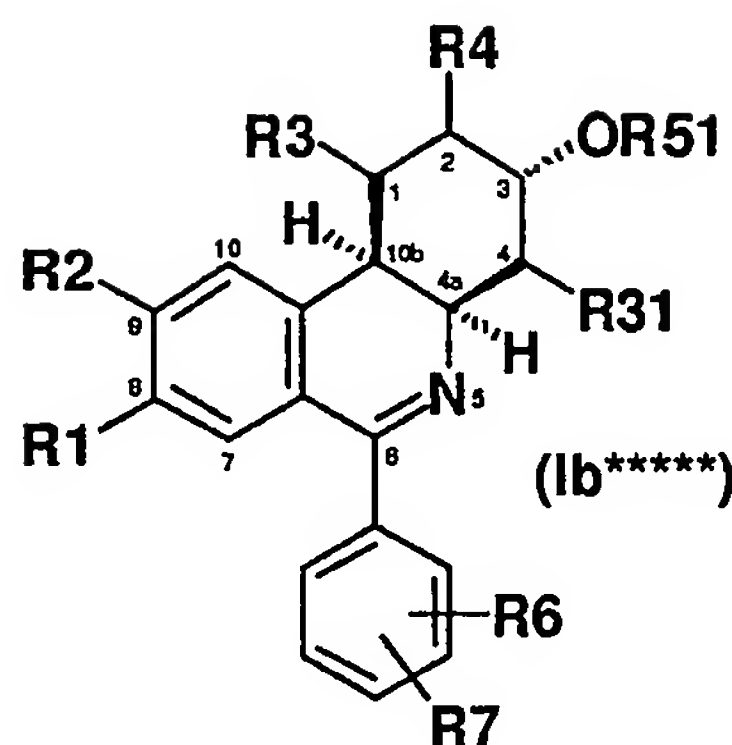
If, for example in compounds of the formula Ib** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is R in the position 3, R in the position 4a and R in the position 10b.

If, for example in compounds of the formula Ib*** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is S in the position 3, S in the position 4a and S in the position 10b.

If, for example in compounds of the formula Ib**** R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is R in the position 3, S in the position 4a and S in the position 10b.

More preferred compounds of the formula I according to embodiment b are those which have, with respect to the positions 3, 4a and 10b, the same configuration as shown in the formula Ib****:

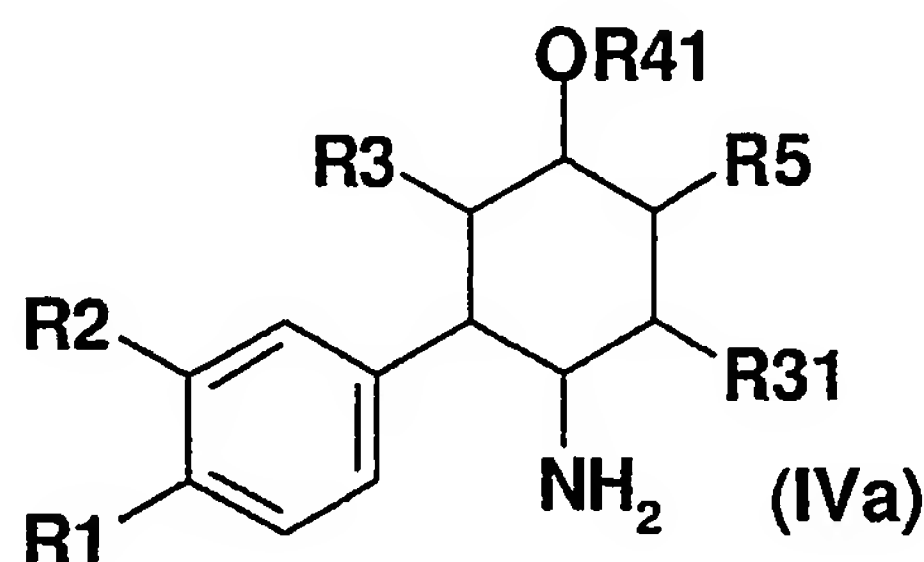
- 14 -



If, for example in compounds of the formula Ib*****, R3, R31 and R5 have the meaning hydrogen, then the configuration – according the rules of Cahn, Ingold and Prelog – is S in the position 3, R in the position 4a and R in the position 10b.

Within the meaning of the embodiments a and b according to this invention, compounds of formula Ia***** are in particular to be emphasized.

The enantiomers can be separated in a manner known per se (for example by preparation and separation of appropriate diastereoisomeric compounds). Thus, e.g. an enantiomer separation can be carried out at the stage of the starting compounds having a free amino group such as starting compounds of formulae IVa or VIIb as defined below.



Separation of the enantiomers can be carried out, for example, by means of salt formation of the racemic compounds of the formulae IVa or VIIb with optically active acids, preferably carboxylic acids, subsequent resolution of the salts and release of the desired compound from the salt. Examples of optically active carboxylic acids which may be mentioned in this connection are the enantiomeric forms of mandelic acid, tartaric acid, O,O'-dibenzoyltartaric acid, camphoric acid, quinic acid, glutamic acid, pyroglutamic acid, malic acid, camphorsulfonic acid, 3-bromocamphorsulfonic acid, α -methoxyphenylacetic acid, α -methoxy- α -trifluoromethylphenylacetic acid and 2-phenylpropionic acid. Alternatively, enantiomerically pure starting compounds can be prepared via asymmetric syntheses. Enantiomerically pure starting

compounds as well as enantiomerically pure compounds of the formula I can be also obtained by chromatographic separation on chiral separating columns; by derivatization with chiral auxiliary reagents, subsequent diastereomer separation and removal of the chiral auxiliary group; or by (fractional) crystallization from a suitable solvent.

The compounds according to the invention can be prepared, for example, as shown in the reaction schemes below and according to the following specified reaction steps, or, particularly, in a manner as described by way of example in the following examples, or analogously or similarly thereto according to preparation procedures or synthesis strategies known to the person skilled in the art.

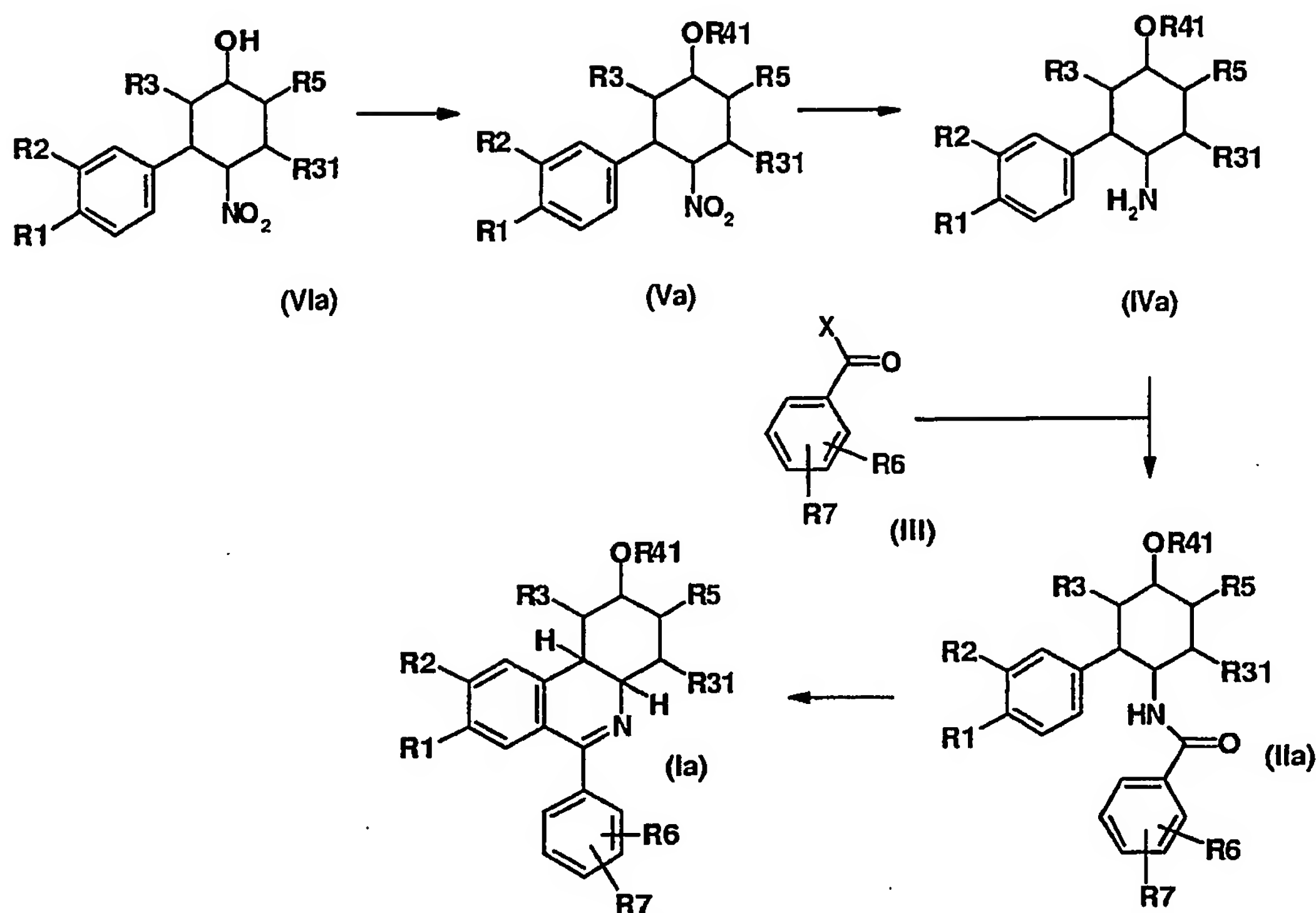
Compounds of formula I, in which R1, R2, R3, R31, R4, R5, R6 and R7 have the meanings mentioned above, according to embodiment a or b (i.e. compounds of formulae Ia or Ib, respectively) can be obtained as described as follows.

Compounds of formula Ia according to embodiment a can be prepared as described and shown in reaction scheme 1 below.

In the first reaction step of the synthesis route shown in scheme 1, compounds of the formula Va, in which R1, R2, R3, R31, R41 and R5 have the meanings mentioned above in embodiment a whereby R41 is other than hydrogen, are prepared from the corresponding compounds of the formula VIa by introduction of the group R41, which is other than hydrogen. The introduction reaction is carried out in a manner habitual per se for an etherification or esterification reaction, or as described by way of example in the following examples.

Reaction scheme 1:

- 16 -



In the next reaction step of the synthesis route shown in reaction scheme 1, the nitro group of compounds of the formula Va, in which R₁, R₂, R₃, R₃₁, R₄₁ and R₅ have the meanings mentioned above in embodiment a whereby R₄₁ is other than hydrogen, is reduced to the amino group of the corresponding compounds of the formula IVa. Said reduction is carried out in a manner known to the person skilled in the art, for example as described in J. Org. Chem. 1962, 27, 4426 or as described in the following examples. In more detail, the reduction can be carried out, for example, by catalytic hydrogenation, e.g. in the presence of Raney nickel or a noble metal catalyst such as palladium on active carbon, in a suitable solvent such as methanol or ethanol at room temperature and under normal or elevated pressure. Optionally, a catalytic amount of an acid, such as, for example, hydrochloric acid, can be added to the solvent. Preferably, however, the reduction is carried out using a hydrogen-producing mixture, for example, metals such as zinc, zinc-copper couple or iron with organic acids such as acetic acid or mineral acids such as hydrochloric acid. More preferably, the reduction is carried out using a zinc-copper couple in the presence of an organic or an inorganic acid. Such a zinc-copper couple is accessible in a way known to the person of ordinary skill in the art.

Compounds of the formula IVa, in which R₁, R₂, R₃, R₃₁, R₄₁ and R₅ have the meanings indicated above in embodiment a whereby R₄₁ is other than hydrogen and which are sensitive against catalytic hydrogenation, can be prepared from the corresponding compounds of the formula Va by selective reduction of the nitro group in a manner known to the person skilled in the art, for example by hydrogen transfer reaction in the presence of a metal catalyst, for example palladium or, preferably, Raney nickel, in a lower

alcohol as solvent using, for example, ammonium formate or, preferably, hydrazine hydrate as hydrogen donor.

Compounds of the formula IIa, in which R1, R2, R3, R31, R41, R5, R6 and R7 have the meanings indicated above in embodiment a whereby R41 is other than hydrogen, are accessible from the corresponding compounds of the formula IVa by reaction with corresponding compounds of the formula III, in which X represents a suitable leaving group, preferably a chlorine atom.

Alternatively, compounds of the formula IIa can also be prepared from the corresponding compounds of the formula IVa and corresponding compounds of the formula III, in which X is hydroxyl, by reaction with amide bond linking reagents known to the person skilled in the art. Exemplary amide bond linking reagents known to the person skilled in the art which may be mentioned are, for example, the carbodiimides (e.g. dicyclohexylcarbodiimide or, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), azodicarboxylic acid derivatives (e.g. diethyl azodicarboxylate), uronium salts [e.g. O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate] and N,N'-carbonyldiimidazole. In the scope of this invention preferred amide bond linking reagents are uronium salts and, particularly, carbodiimides, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

Compounds of the formula III are either known or can be prepared in a known manner.

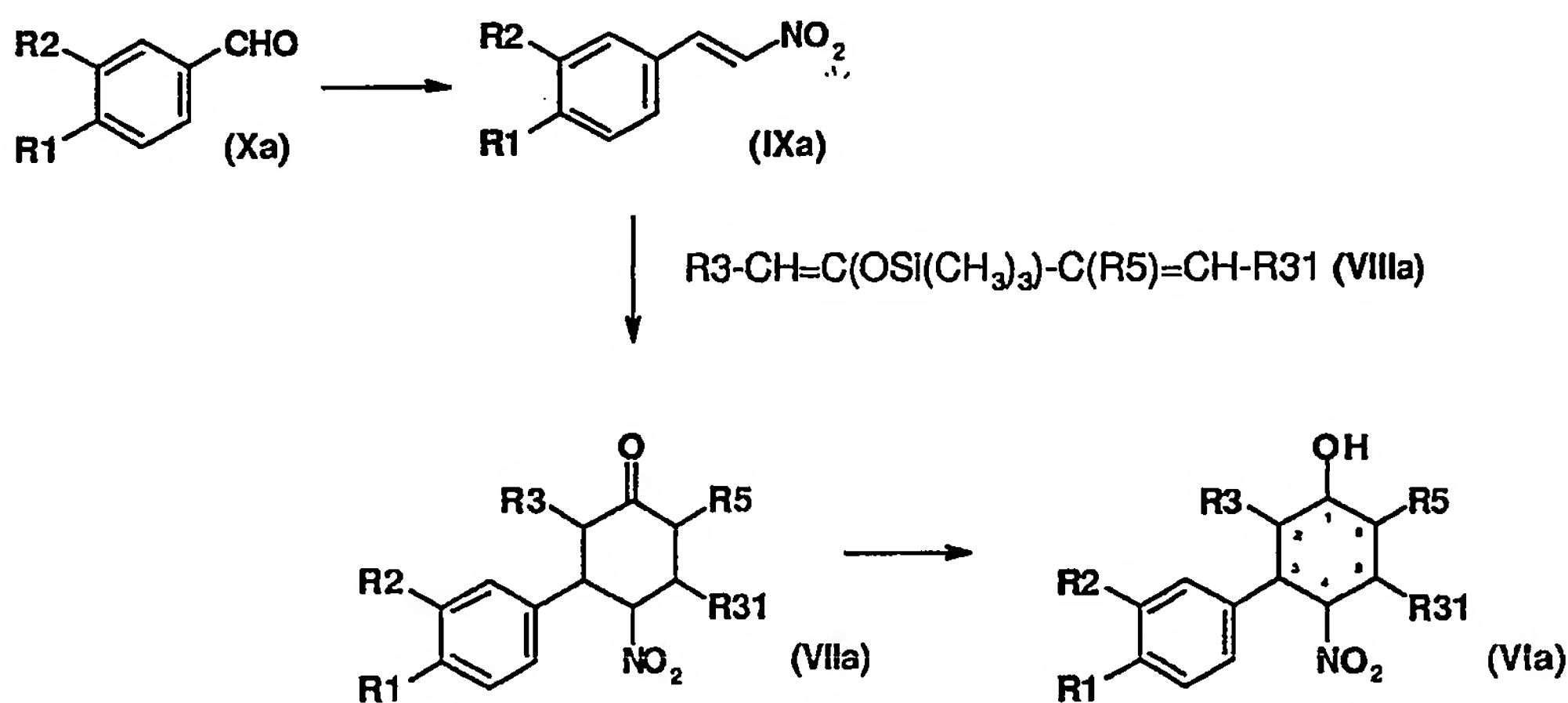
Compounds of the formula Ia, in which R1, R2, R3, R31, R41, R5, R6 and R7 have the meanings mentioned in embodiment a whereby R41 is other than hydrogen, can be obtained by cyclocondensation of corresponding compounds of the formula IIa.

Said cyclocondensation reaction is carried out in a manner known per se to the person skilled in the art or as described by way of example in the following examples, according to Bischler-Napieralski (e.g. as described in J. Chem. Soc., 1956, 4280-4282) in the presence of a suitable condensing agent, such as, for example, polyphosphoric acid, phosphorus pentachloride, phosphorus pentoxide or phosphorus oxychloride, in a suitable inert solvent, e.g. in a chlorinated hydrocarbon such as chloroform, or in a cyclic hydrocarbon such as toluene or xylene, or another inert solvent such as isopropyl acetate or acetonitrile, or without further solvent using an excess of condensing agent, at reduced temperature, or at room temperature, or at elevated temperature or at the boiling temperature of the solvent or condensing agent used. If necessary, said cyclocondensation reaction can be carried out in the presence of one or more suitable Lewis Acids such as, for example, suitable metal halogenides (e.g. chlorides) or sulphonates (e.g. triflates), including rare earth metal salts, such as e.g. anhydrous aluminum trichloride, aluminum tribro-

mide, zinc chloride, boron trifluoride etherate, titanium tetrachloride or, in particular, tin tetrachloride, and the like.

Below reaction scheme 2 shows the synthesis of compounds of the formula VIa, in which R1, R2, R3, R31 and R5 have the meanings indicated above in embodiment a, from corresponding compounds of the formula VIIa via reduction reaction of the carbonyl group. Suitable reducing agents for the abovementioned reduction reaction may include, for example, metal hydride compounds such as, for example, diisopropylaluminium hydride, borane, sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride, zinc borohydride, potassium tri-sec-butylborohydride, sodium tri-sec-butylborohydride, lithium tri-sec-butylborohydride, β -isopinocampheyl-9-borabicyclo[3.3.1]nonane and the like. The preferred examples of said reducing agents are sodium cyanoborohydride, β -isopinocampheyl-9-borabicyclo[3.3.1]nonane and potassium tri-sec-butylborohydride. The most preferred examples of the abovementioned reducing agents are β -isopinocampheyl-9-borabicyclo[3.3.1]nonane and potassium tri-sec-butylborohydride, which both allow to prepare compounds of the formula VIa stereoselectively. "Stereoselectively" in this connection means that those compounds of the formula VIa, in which the hydrogen atoms in positions 1 and 3 are located at the opposite side of the plane defined by the cyclohexane ring, are obtained preferentially.

Reaction scheme 2:



The compounds of the formula VIIa, in which R1, R2, R3, R31 and R5 have the meanings mentioned in embodiment a, are either known or can be obtained by the reaction of compounds of the formula IXa, in which R1 and R2 have the meanings mentioned above, with compounds of the formula VIIIa, in which R3, R31 and R5 have the meanings mentioned above in embodiment a. The cycloaddition reaction is carried out in a manner known to the person skilled in the art according to Diels-Alder, e.g. as described in J.

Amer. Chem. Soc. 1957, 79, 6559 or in J. Org. Chem. 1952, 17, 581 or as described in the following examples.

Compounds of the formulae VIa or Va, in which the phenyl ring and the nitro group are trans to one another, can be converted in a manner known to the person skilled in the art into the corresponding cis compounds, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6559 or as described in the following examples.

The compounds of the formulae VIIIa and IXa are either known or can be prepared in a known manner. The compounds of the formula IXa can be prepared, for example, in a manner known to the person skilled in the art from corresponding compounds of the formula Xa as described, for example, in J. Chem. Soc. 1951, 2524 or in J. Org. Chem. 1944, 9, 170 or as described in the following examples.

The compounds of the formula Xa, in which R1 and R2 have the meanings indicated above in embodiment a, are either known or can be prepared in a manner known to the person skilled in the art, as described, for example, in Ber. Dtsch. Chem. Ges. 1925, 58, 203.

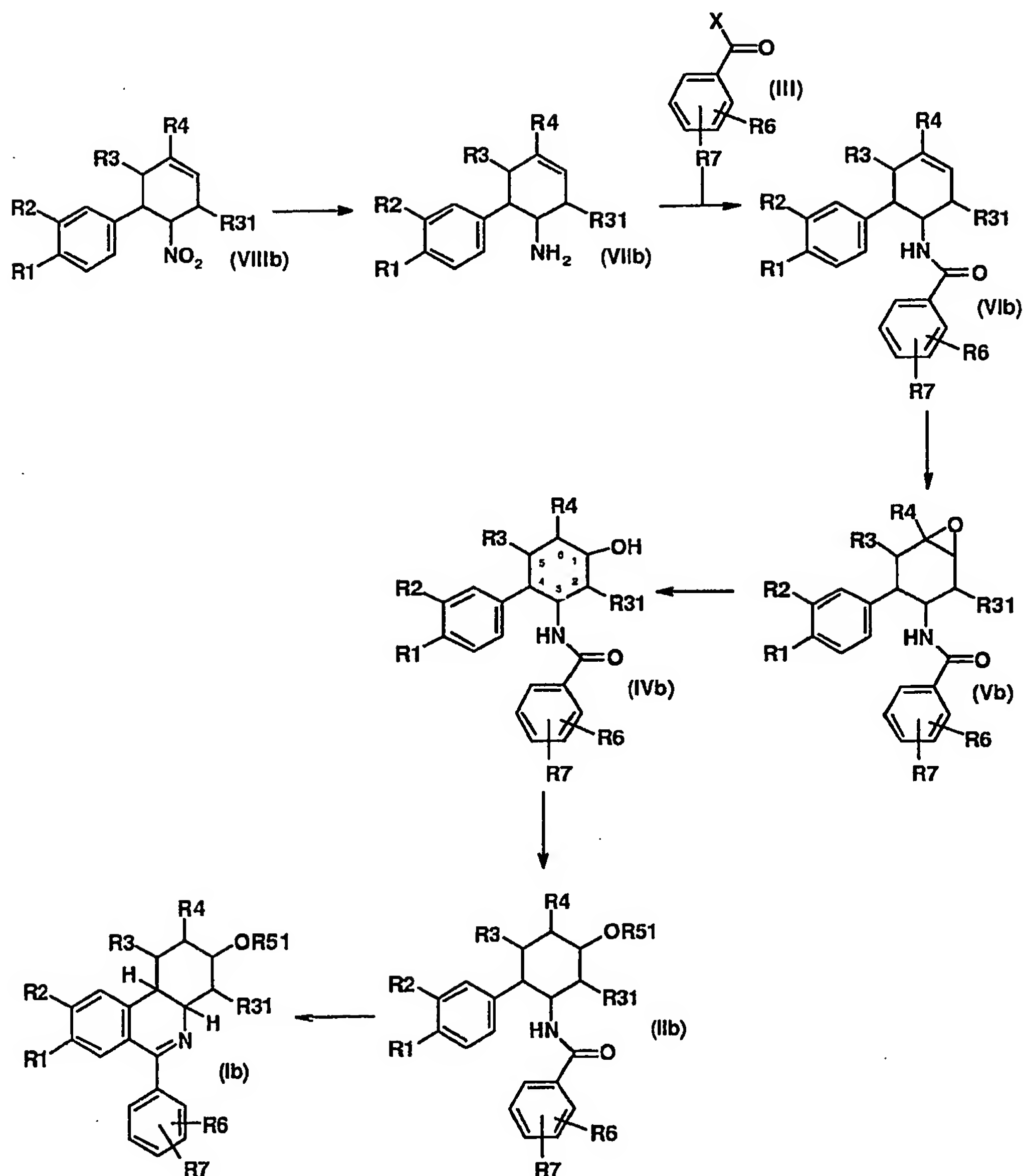
Compounds of formula Ib according to embodiment b, in which R1, R2, R3, R31, R4 and R51 have the meanings indicated above in embodiment b whereby R51 is other than hydrogen, can be prepared as described and shown in reaction scheme 3 below.

In the first reaction step in reaction scheme 3, the nitro group of compounds of the formula VIIIb, in which R1, R2, R3, R31 and R4 have the meanings indicated in embodiment b above, is reduced to obtain corresponding compounds of the formula VIIb. Said reduction reaction is carried out in a manner known to the person skilled in the art, for example as described in J. Org. Chem. 1962, 27, 4426 or as described in the following examples. More specifically, the reduction can be carried out, for example, by contacting compounds of the formula VIIIb with a hydrogen-producing mixture such as, preferably, metallic zinc in a mildly acidic medium such as acetic acid in a lower alcohol such as methanol or ethanol at room temperature or at elevated temperature or, preferably, at the boiling temperature of the solvent mixture. Alternatively, the reduction can be carried out by selective reduction of the nitro group in a manner known to the person skilled in the art, for example by hydrogen transfer reaction in the presence of a metal catalyst, for example palladium or preferably Raney nickel, in a suitable solvent, preferably a lower alcohol, using, for example ammonium formate or preferably hydrazine hydrate as hydrogen donor.

Compounds of the formula VIIb obtained can be reacted, for example, as described by way of example in the following examples with compounds of the formula III, in which R6 and R7 have the meanings given

above and X represents a suitable leaving group, preferably a chlorine atom, to give corresponding compounds of the formula VIb.

Reaction scheme 3:



Alternatively, compounds of the formula VIb, in which R_1 , R_2 , R_3 , R_{31} , R_4 , R_6 and R_7 have the meanings given above in embodiment b, can also be prepared, for example, from corresponding compounds of the formula VIIb and corresponding compounds of the formula III, in which X is hydroxyl, by reaction with amide bond linking reagents known to the person skilled in the art. Exemplary amide bond linking reagents

known to the person skilled in the art which may be mentioned are, for example, the carbodiimides (e.g. dicyclohexylcarbodiimide or, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), azodicarboxylic acid derivatives (e.g. diethyl azodicarboxylate), uronium salts [e.g. O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate] and N,N'-carbonyldiimidazole. In the scope of this invention preferred amide bond linking reagents are uronium salts and, particularly, carbodiimides, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

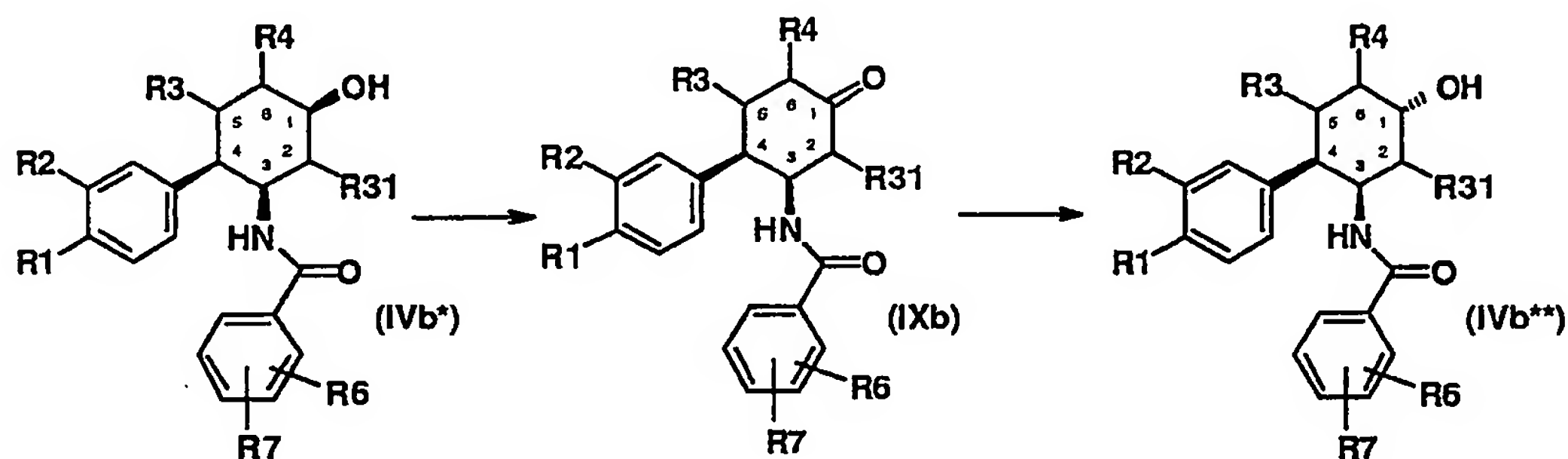
In the next step compounds of the formula Vlb are converted into corresponding compounds of the formula Vb by epoxidation reaction, which can be carried out as described in the following examples or in a manner known to one of ordinary skill in the art employing, for example, suitable epoxidation methods or suitable epoxidation reagents such as, for example, peracids (e.g. m-chloroperbenzoic acid) or organic or inorganic peroxides (e.g. dimethyldioxirane, hydrogen peroxide or persulfates).

Compounds of the formula Vb obtained can be reduced by art-known methods to corresponding compounds of the formula IVb. More specifically, said reduction reaction can be performed employing, for example, as described by way of example in the following examples sodium borohydride as reductant. Alternatively, said reduction reaction can be also carried out using, for example, lithium aluminium hydride or a reductive mixture comprising noble metals, such as platinum dioxide or palladium, and a suitable hydrogen donor. With the aid of each of those said reduction methods, compounds of the formula Vb can be converted largely regio- and diastereoselectively into compounds of the formula IVb, wherein the hydroxyl radical in position 1 and the amido radical in position 3 are located at the same side of the plane defined by the cyclohexane ring.

It is moreover known to one of ordinary skill of the art, that the absolute configuration of a chiral carbon atom, preferably, to which a hydroxyl group and a hydrogen atom are bonded, can be inverted. Thus the configuration of the carbon atom in position 1 of compounds of the formula IVb can be optionally inverted. Said inversion of configuration of position 1 of compounds of the formula IVb can be achieved in a manner familiar to the person skilled in the art, for example by derivatization of position 1 with a suitable leaving group and subsequent replacement of said leaving group by a suitable nucleophile in a nucleophilic substitution reaction according to SN2 mechanism. Alternatively, said inversion of configuration of position 1 of compounds of the formula IVb can be also obtained, for example, as described by way of example in the following examples according to subsequently specified two step procedure shown in reaction scheme 4 below. In more detail, in the first step of said procedure shown in reaction scheme 4, exemplary compounds of the formula IVb*, in which R1, R2, R6 and R7 have the meanings indicated above in embodiment b, and R3, R31 and R4 are hydrogen and position 1 has the R configuration, are converted by oxidation reaction into corresponding compounds of the formula IXb. Said oxidation is likewise carried

out under conditions customary per se using, for example, chloranil, atmospheric oxygen, manganese dioxide or, preferably, chromium oxides as an oxidant. Then in the second step, compounds of the formula IXb obtained are converted by art-known reduction reaction of the keto group, preferably with metal hydride compounds or, more specifically, metal borohydrides, such as, for example, sodium borohydride, into corresponding compounds of formula IVb**, in which position 1 has now S configuration and thus the configuration of the carbon atom in position 1 is now inverted regarding to said compounds of the formula IVb*.

Reaction scheme 4:

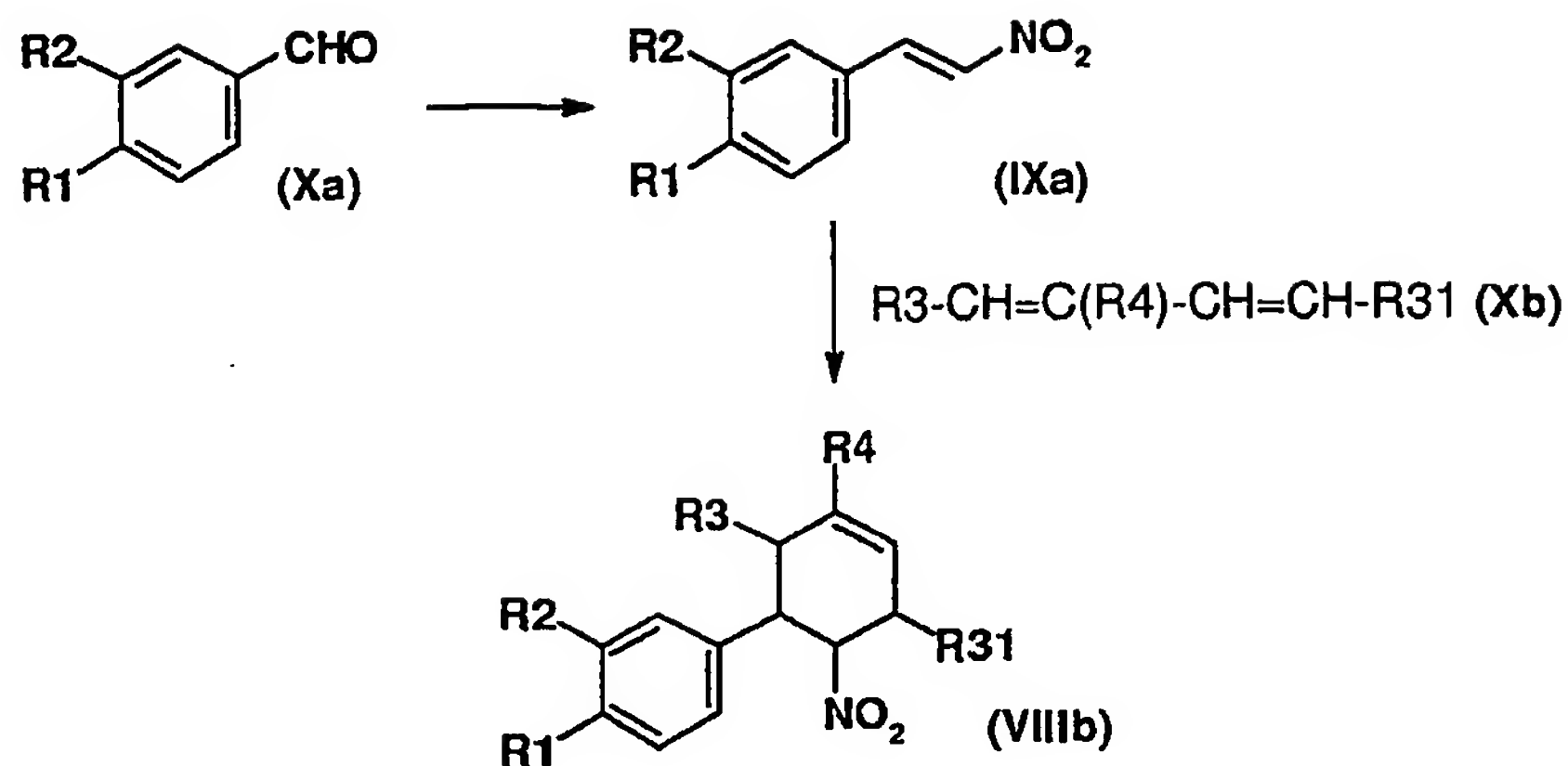


In the next reaction step of the synthesis route shown in reaction scheme 3 shown above, compounds of the formula IVb are converted into corresponding compounds of the formula IIb by introduction of the group R51 whereby R51 is other than hydrogen. The introduction reaction is carried out in a manner habitual per se (e.g. via alkylation or acylation reaction) or as described by way of example in the following examples.

The cyclization reaction leading to compounds of the formula Ib, in which R1, R2, R3, R31, R4, R51, R6 and R7 have the meanings given above in embodiment b whereby R51 is other than hydrogen, can be carried out, for example, as described by way of example in the following examples or analogously or similarly thereto, or as mentioned above for compounds according to embodiment a.

Compounds of the formula VIIIb, in which R1, R2, R3, R31 and R4 have the meanings mentioned above in embodiment b, are either known or can be obtained, for example as shown in reaction scheme 5, by the reaction of compounds of the formula IXa, in which R1 and R2 have the abovementioned meanings, with compounds of the formula Xb, in which R3, R31 and R4 have the meanings indicated above in embodiment b.

Reaction scheme 5:



The cycloaddition is in this case carried out in a manner known to the person skilled in the art according to Diels-Alder, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6559 or in J. Org. Chem. 1952, 17, 581 or as described in the following examples.

Compounds of the formula VIIIb, in which the phenyl ring and the nitro group are trans to one another, can be converted such as known to the person skilled in the art into the corresponding cis compounds, e.g. as described in J. Amer. Chem. Soc. 1957, 79, 6559 or as described in the following examples.

The compounds of the formula Xb are either known or can be prepared in a known manner.

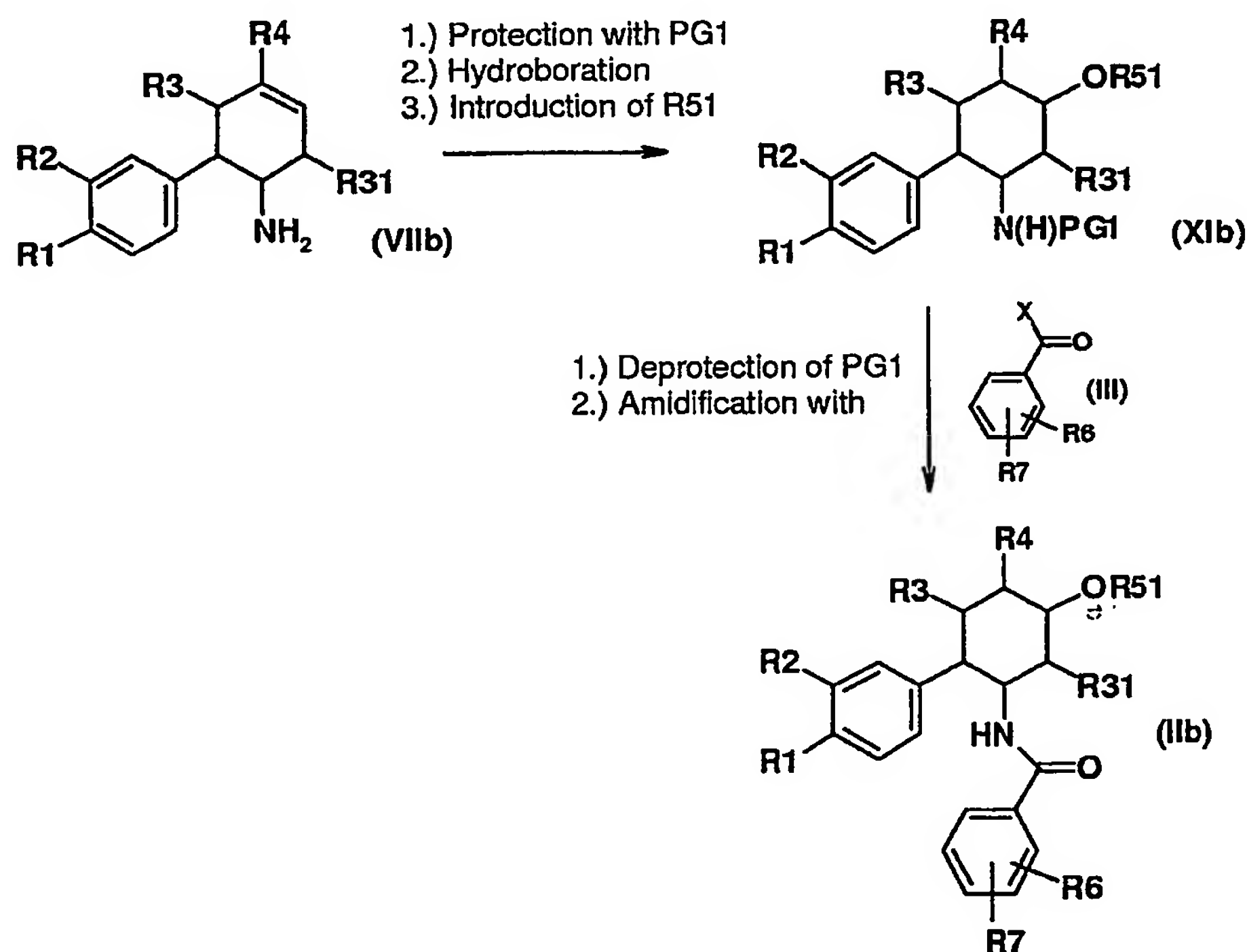
In an alternative, compounds of the formula IIb, in which R1, R2, R3, R31, R4, R51, R6 and R7 have the meanings given above in embodiment b whereby R51 is other than hydrogen (particularly compounds of formula IIb, in which R1, R2, R51, R6 and R7 have the meanings given above in embodiment b whereby R51 is other than hydrogen, and R3, R31 and R4 are all hydrogen) can also be obtained as shown in reaction scheme 6 and as described by way of example in the following examples.

In the first reaction step of the route outlined in reaction scheme 6, the amino group of compounds of the formula VIIb is protected with an art-known protective group PG1, such as e.g. the tert-butoxycarbonyl group. The protected compounds are subjected to hydroboration reaction to obtain over two steps compounds of formula XIb. Said hydroboration reaction is carried out as described in the following examples using an appropriate (hydro)borating agent, such as e.g. 9-BBN, isopinocampheylborane or the like, or, particularly, borane-tetrahydrofuran (H₃B-THF), advantageously at ambient temperature. The compounds obtained are then converted into compounds of the formula XIb by introduction of the group R51 whereby R51 is other than hydrogen in a manner analogously as described above.

In the next reaction step of the synthesis route shown in reaction scheme 6, compounds of formula XIb are converted into corresponding compounds of the formula IIb by deprotection of the protective group PG1 and amidification with compounds of the formula III. Said reactions are carried out in a manner habitual per se or as described in the specification of this invention or in the following examples.

If necessary, the product obtained via said hydroboration reaction or, suitably, the R51-substituted derivative thereof is purified from resulting stereo- and/or regioisomeric side products by methods known to the person skilled in the art, such as e.g. by chromatographic separation techniques.

Reaction scheme 6:



Optionally, compounds of the formula I can be also converted into further compounds of the formula I by methods known to one of ordinary skill in the art. More specifically, for example, from compounds of the formula I in which

- R41 or R51 is hydrogen, the corresponding ester compounds can be obtained by esterification reactions;
- R41 or R51 is hydrogen, the corresponding ether compounds can be obtained by etherification reactions;
- R41 or R51 is an acyl group, such as e.g. acetyl, the corresponding hydroxyl compounds can be obtained by deesterification (e.g. saponification) reactions;

- 25 -

- d) R6 is a nitro group, the corresponding amino group can be obtained by reduction reaction using a suitable reducing agent.

The methods mentioned under a), b), c) and d) are expediently carried out analogously to the methods known to the person skilled in the art or as described by way of example in the following examples.

Optionally, compounds of the formula I can be converted into their salts, or, optionally, salts of the compounds of the formula I can be converted into the free compounds.

In addition, the compounds of the formula I can be converted, optionally, into their N-oxides, for example with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in dichloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with the reaction conditions which are specifically necessary for carrying out the N-oxidation.

It is moreover known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3rd Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

The substances according to the invention are isolated and purified in a manner known per se, for example by distilling off the solvent under reduced pressure and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low-molecular-weight aliphatic alcohol, such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted into the free compounds, which can in turn be converted into salts, by alkalization or by acidification. In this manner, pharmacologically unacceptable salts can be converted into pharmacologically acceptable salts.

Suitably, the conversions mentioned in this invention can be carried out analogously or similarly to methods which are familiar per se to the person skilled in the art.

The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for compounds of the formula I. All these other possible synthesis routes are also part of this invention.

Having described the invention in detail, the scope of the present invention is not limited only to those described characteristics or embodiments. As will be apparent to persons skilled in the art, modifications, analogies, variations, derivations, homologisations and adaptations to the described invention can be made on the base of art-known knowledge and/or, particularly, on the base of the disclosure (e.g. the explicit, implicit or inherent disclosure) of the present invention without departing from the spirit and scope of this invention as defined by the scope of the appended claims.

The following examples serve to illustrate the invention further without restricting it. Likewise, further compounds of the formula I, whose preparation is not explicitly described, can be prepared in an analogous or similar manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

Any or all of the compounds of formula I according to the present invention which are mentioned in the following examples as final compounds as well as their salts, N-oxides and salts of the N-oxides are a preferred subject of the present invention.

In the examples, m.p. stands for melting point, h for hour(s), min for minutes, R_f for retention factor in thin layer chromatography, s.p. for sintering point, EF for empirical formula, MW for molecular weight, MS for mass spectrum, M for molecular ion, fnd. for found, calc. for calculated, other abbreviations have their meanings customary per se to the skilled person.

According to common practice in stereochemistry, the symbols RS and SR are used to denote the specific configuration of each of the chiral centers of a racemate. In more detail, for example, the term "(2RS,4aRS,10bRS)" stands for a racemate (racemic mixture) comprising the one enantiomer having the configuration (2R,4aR,10bR) and the other enantiomer having the configuration (2S,4aS,10bS).

Examples

Final Compounds

1. (2RS,4aRS,10bRS)-9-(2,2-Difluoroethoxy)-6-(4-fluorophenyl)-8-methoxy-(1,2,3,4,4a,10b)-hexahydrophenanthridin-2-ol

147 mg of cesium carbonate are added to 777 mg of acetic acid (2RS,4aRS,10bRS)-9-(2,2-difluoroethoxy)-6-(4-fluorophenyl)-8-methoxy-(1,2,3,4,4a,10b)-hexahydrophenanthridin-2-yl ester (compound 2) dissolved in 4 ml of dichloromethane and 13 ml of methanol are added. The solution is stirred for 18 h. The reaction mixture is adsorbed to 3 g of silica and purified by flash chromatography to give 624 mg of the title compound.

2. Acetic acid (2RS,4aRS,10bRS)-9-(2,2-difluoroethoxy)-6-(4-fluorophenyl)-8-methoxy-(1,2,3,4,4a,10b)-hexahydrophenanthridin-2-yl ester

930 mg of acetic acid (1RS,3RS,4RS)-4-[[1-(4-fluorophenyl)methanoyl]amino]-3-[3-(2,2-difluoroethoxy)-4-methoxyphenyl]cyclohexyl ester (compound A1) are dissolved in 2 ml of phosphorus oxychloride and heated at 100°C for 5h. 15 ml of dichloromethane are added and the mixture poured into 15 ml of aqueous sodium hydroxide (10M strength) with cooling by an ice bath. Water is added and the pH adjusted to 9-10 by adding aqueous hydrochloric acid (3M strength) dropwise. After reextraction with dichloromethane the organic layer is dried over magnesium sulfate and the crude product purified by flash chromatography to give 852 mg of the title compound.

3. 4-[(2RS,4aRS,10bRS)-9-(2,2-Difluoro-ethoxy)-2-hydroxy-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-6-yl]-benzonitrile

Starting from acetic acid (2RS,4aRS,10bRS)-6-(4-cyano-phenyl)-9-(2,2-difluoro-ethoxy)-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester (compound 4) the title compound is obtained according to the procedure as in Example 1.

EF: C23 H22 F2 N2 O3; MW: calc.: 412.44

MS: fnd.: 413.2 (MH⁺)

4. Acetic acid (2RS,4aRS,10bRS)-6-(4-cyano-phenyl)-9-(2,2-difluoro-ethoxy)-8-methoxy-1,2,3,4,4a,10b-hexahydro-phenanthridin-2-yl ester

Starting from acetic acid (1RS,3RS,4RS)-4-[[1-(4-cyano-phenyl)methanoyl]amino]-3-[3-(2,2-difluoro-ethoxy)-4-methoxyphenyl]cyclohexyl ester (compound A2) the title compound is obtained according to the procedure as in Example 2.

Starting from the appropriate starting compounds further final compounds can be prepared analogously or similarly as described herein.

Starting Compounds

A1. Acetic acid (1RS,3RS,4RS)-4-[[1-(4-fluorophenyl)methanoyl]amino]-3-[3-(2,2-difluoro-ethoxy)-4-methoxyphenyl]cyclohexyl ester

490 mg of 4-fluorobenzoic acid, 670 mg of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and 2 mg of 4-dimethylaminopyridine are placed in a flask under nitrogen. 1000 mg of acetic acid (1RS,3RS,4RS)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester (compound B1) dissolved in 10 ml of dichloromethane are added and the solution stirred for 72 h. The reaction is quenched with 10 ml of water. After phase separation the organic layer is washed with 2 ml of saturated KHCO_3 -solution and the water layer reextracted with dichloromethane. After drying the organic layer with sodium sulfate the residue is purified by chromatography to give 1.21 g of the title compound.

A2. Acetic acid (1RS,3RS,4RS)-4-[[1-(4-cyanophenyl)methanoyl]amino]-3-[3-(2,2-difluoro-ethoxy)-4-methoxyphenyl]cyclohexyl ester

Starting from acetic acid (1RS,3RS,4RS)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester (compound B1) and the appropriate carboxylic acid the title compound is obtained according to the procedure as in compound A1.

B1. Acetic acid (1RS,3RS,4RS)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester

The title compound is prepared analogously as described in Example B2 starting from starting compound C1 mentioned below.

B1a. Acetic acid (1R,3R,4R)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester

The title compound can be obtained from its pyroglutamate salt (compound B1b) using sodium hydrogen-carbonate solution in a water/dichloromethane mixture.

B1b. Acetic acid (1R,3R,4R)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester, salt with L-pyroglutamic acid

343 mg (1.00 mmol) of acetic acid (1RS,3RS,4RS)-4-amino-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-cyclohexyl ester (compound B1) are dissolved in 3 ml of isopropanol. A solution of 103 mg (0.80 mmol) of

L-pyroglutamic acid in 2 ml of isopropanol is added. After filtering and drying 162 mg of the pyroglutamate are isolated with an enantiomeric ratio of 97 : 3 in favour of the title compound.

B2. Acetic acid (1RS,3RS,4RS)-4-amino-3-(3,4-dimethoxyphenyl)cyclohexyl ester

A solution of 10.37 g of acetic acid (1RS,3RS,4RS)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexyl ester (compound C2) in 240 ml of ethanol is added to a zinc-copper couple, prepared from 16.8 g of zinc powder and 920 mg of copper (II) acetate monohydrate in acetic acid, the resulting suspension is refluxed and treated with 26 ml of acetic acid, 3.2 ml of water and 26 ml of ethanol. The resulting mixture is refluxed for further 15 min. The precipitate is filtered off with suction and the solvent is removed. Chromatographical purification on silica gel using a mixture of petroleum ether/ethyl acetate/triethylamine in the ratio 2/7/1 and concentration of the corresponding eluate fractions afford 5.13 g (55 % of theory) of the title compound as a pale brown oil.

$R_f = 0.35$ (petroleum ether/ethyl acetate/triethylamine = 2/7/1)

C1. Acetic acid (1RS,3RS,4RS)-3-[3-(2,2-difluoro-ethoxy)-4-methoxy-phenyl]-4-nitrocyclohexyl ester

The title compound is prepared analogously as described in Example C2 starting from starting compound D1 mentioned below.

C2. Acetic acid (1RS,3RS,4RS)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexyl ester

10.18 g of (1RS,3RS,4RS)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexanol (compound D2) are dissolved in 100 ml of acetic anhydride and the solution is heated to 100°C for 1-2 h. After removal of the solvent, the residue is chromatographed on silica gel using a mixture of petroleum ether/ethyl acetate in the ratio 2/1. Concentration of the corresponding eluate fractions furnish 10.37 g (89 % of theory) of the title compound as an oil.

$R_f = 0.32$ (petroleum ether/ethyl acetate = 2/1)

D1. (1RS,3RS,4RS)-3-[3-(2,2-Difluoro-ethoxy)-4-methoxy-phenyl]-4-nitrocyclohexanol

The title compound is prepared analogously as described in Example D2 starting from starting compound E1 mentioned below.

D2. (1RS,3RS,4RS)-3-(3,4-Dimethoxyphenyl)-4-nitrocyclohexanol

10 g of (1RS,3RS,4SR)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexanol (compound E2) are dissolved in 170 ml of absolute 1,2-dimethoxyethane. 14.3 ml of a 30 % solution of sodium methanolate in methanol are added dropwise. After complete addition, stirring is continued for 10 min and a mixture consisting of 85 % phosphoric acid and methanol is added to pH 1. By adding of saturated potassium hydrogencarbonate solution the resulting suspension is neutralized. The mixture is diluted with water and dichloromethane,

- 30 -

the organic layer is separated and extracted with dichloromethane. The solvents are removed under reduced pressure to yield the title compound as a pale yellow oil, which crystallizes. The title compound is used without further purification in the next step.

$R_f = 0.29$ (petroleum ether/ethyl acetate = 1/1)

M.p.: 126-127 °C

E1. (1RS,3RS,4SR)-3-[3-(2,2-Difluoro-ethoxy)-4-methoxy-phenyl]-4-nitrocyclohexanol

The title compound is prepared analogously as described in Example E2 starting from starting compound F1 mentioned below.

E2. (1RS,3RS,4SR)-3-(3,4-Dimethoxyphenyl)-4-nitrocyclohexanol

Under nitrogen atmosphere 16.76 g of (3RS,4SR)-3-(3,4-dimethoxyphenyl)-4-nitrocyclohexanone (compound F2) are dissolved in 300 ml of tetrahydrofurane, the solution is cooled to -78 °C, and 75 ml of 1 M solution of potassium tri-sec-butylborohydride in tetrahydrofurane is added dropwise. After stirring for further 1 h, a mixture consisting of 30% hydrogeneperoxide solution and phosphate buffer solution is added. Stirring is continued for further 10 min, the reaction mixture is diluted with 400 ml of ethyl acetate and the aqueous layer is extracted with ethyl acetate, the combined organic phases are concentrated to give a foam, which is purified by chromatography on silica gel using a mixture of petroleum ether/ethyl acetate in the ratio 1/1 to furnish 10.18 g (60 % of theory) of the title compound.

EF: $C_{14}H_{19}NO_5$; MW: 281.31

MS: 299.1 (MNH_4^+)

$R_f = 0.29$ (petroleum ether/ethyl acetate = 1/1)

M.p.: 139-141 °C

F1. (3RS,4SR)-3-[3-(2,2-Difluoro-ethoxy)-4-methoxy-phenyl]-4-nitrocyclohexanone

The title compound is prepared analogously as described in Example F2 starting from starting compound G1 mentioned below.

F2. (3RS,4SR)-3-(3,4-Dimethoxyphenyl)-4-nitrocyclohexanone

90.0 g of 3,4-dimethoxy- ω -nitrostyrene (compound G2), 90 ml of 2-trimethylsilyloxy-1,3-butadiene and 180 ml of abs. toluene are put in an autoclave, where the mixture is stirred at 140 °C for 2 days and then cooled. After addition of 1000 ml of ethyl acetate, 300 ml of a 2 N solution of hydrochloric acid are dropped under stirring. The phases are separated and the aqueous layer is extracted three times with dichloromethane. The combined organic extracts are washed with saturated sodium hydrogencarbonate solution, dried over magnesium sulfate and the solvents are removed under reduced pressure to give 150 g of the crude title compound. Further purification is carried out by chromatography on silica gel using

- 31 -

petroleum ether/ethyl acetate in the ratio 1/1 as eluent to give 81.5 g (67 % of theory) of the pure title compound.

EF: $C_{14}H_{17}NO_5$; MW: 279.30

MS: 279 (M^+), 297.1 (MNH_4^+)

R_f = 0.47 (petroleum ether/ethyl acetate = 1/1)

M.p.: 147-148°C

G1. 3-(2,2-Difluoro-ethoxy)-4-methoxy- ω -nitrostyrene

The title compound is prepared analogously as described in Example G2 starting from the appropriate starting compound known to the person skilled in the art or obtainable in an art-known manner or analogously or similarly to an art-known manner.

In more detail, 2.0 g of 3-(2,2-difluoro-ethoxy)-4-methoxy-benzaldehyde (compound H1) and 0.92 g of ammonium acetate are placed in a flask and 1.49 ml of nitromethane and 15 ml of glacial acetic acid are added. After 5 hours of stirring at 100 °C another 1 ml of nitromethane are added and the mixture heated for 16 h. The product crystallizes while cooling the reaction mixture and is filtered off and washed with water (3 x 20 ml) to yield 1.88 g of the title compound as a yellow solid after drying.

G2. 3,4-Dimethoxy- ω -nitrostyrene

207.0 g of 3,4-dimethoxybenzaldehyde, 100.0 g of ammonium acetate and 125 ml of nitromethane are heated to boiling for 3-4 h in 1.0 l of glacial acetic acid. After cooling in an ice bath, the precipitate is filtered off with suction, rinsed with glacial acetic acid and petroleum ether and dried. M.p.: 140-141 °C. Yield: 179.0 g.

H1. 3-(2,2-Difluoro-ethoxy)-4-methoxy-benzaldehyde

10.04 g of isovanillin and 15.5 g of potassium carbonate are placed in an autoclave. 50 ml of DMF are added as well as 12.44 g of 2-bromo-1,1-difluoroethane. The autoclave is closed and heated at 60 °C for 20 hrs. Then the solids are filtered off and washed with 120 ml of DMF. About 120 ml of the solvent are distilled off and the residue poured on 200 ml of ice/water, where the product precipitates. After stirring the slurry for 30 minutes the product is filtered off and dried to give 13.69 g of the desired product.

Commercial utility

The compounds according to the invention have useful pharmacological properties which make them industrially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating action but also on account of their respiratory rate- or respiratory drive-increasing action) and for the removal of erectile dysfunction on account of their vascular dilating action, but on the other hand especially for the treatment of disorders, in particular of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes, of the CNS and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. In this context, the compounds according to the invention are distinguished by a low toxicity, a good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine as therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft versus host reaction, allograft rejections, types of shock (septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)) and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and of the ureters in connection with kidney stones. In addition, the compounds of the invention are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease), mem-

- 33 -

ory impairment associated with Parkinson's disease or multiinfarct dementia; and also illnesses of the central nervous system, such as depressions or arteriosclerotic dementia; as well as for enhancing cognition. Yet in addition, the compounds of the invention are useful in the treatment of diabetes mellitus, leukaemia and osteoporosis.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the above mentioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions for treating disorders which are mediated by phosphodiesterases, in particular PDE4-mediated disorders, such as, for example, those mentioned in the specification of this invention or those which are apparent or known to the skilled person.

The invention also relates to the use of the compounds according to the invention for the manufacture of pharmaceutical compositions having PDE4 inhibitory activity.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned comprising one or more of the compounds according to the invention.

The invention yet furthermore relates to compositions comprising one or more compounds according to this invention and a pharmaceutically acceptable carrier. Said compositions can be used in therapy, such as e.g. for treating, preventing or ameliorating one or more of the abovementioned diseases.

The invention still yet furthermore relates to pharmaceutical compositions according to this invention having PDE, particularly PDE4, inhibitory activity.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is

therapeutically effective for antagonizing the effects of the cyclic nucleotide phosphodiesterase of type 4 (PDE4), ameliorating the symptoms of an PDE4-mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating PDE4-mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds of formula 1 according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries, excipients, carriers, vehicles, diluents or adjuvants which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral delivery is preferred.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 μm , advantageously of 2 to 6 μm .

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for PDE inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarily between 0.01 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.003 and 3 mg/kg per day. In another embodiment, the dose for administration by inhalation is between 0.1 and 3 mg per day, and the dose in the case of systemic therapy (p.o. or i.v.) is between 0.03 and 3 mg/kg per day.

Biological investigations

The second messenger cyclic AMP (cAMP) is well-known for inhibiting inflammatory and immunocompetent cells. The PDE4 isoenzyme is broadly expressed in cells involved in the initiation and propagation of inflammatory diseases (H Tenor and C Schudt, in „Phosphodiesterase Inhibitors“, 21-40, „The Handbook of Immunopharmacology“, Academic Press, 1996), and its inhibition leads to an increase of the intracellular cAMP concentration and thus to the inhibition of cellular activation (JE Souness et al., Immunopharmacology 47: 127-162, 2000).

The antiinflammatory potential of PDE4 inhibitors in vivo in various animal models has been described (MM Teixeira, TIPS 18: 164-170, 1997). For the investigation of PDE4 inhibition on the cellular level (in vitro), a large variety of proinflammatory responses can be measured. Examples are the superoxide production of neutrophilic (C Schudt et al., Arch Pharmacol 344: 682-690, 1991) or eosinophilic (A Hatzelmann et al., Brit J Pharmacol 114: 821-831, 1995) granulocytes, which can be measured as luminol-enhanced chemiluminescence, or the synthesis of tumor necrosis factor- α in monocytes, macrophages or dendritic cells (Gantner et al., Brit J Pharmacol 121: 221-231, 1997, and Pulmonary Pharmacol Therap 12: 377-386, 1999). In addition, the immunomodulatory potential of PDE4 inhibitors is evident from the inhibition of T-cell responses like cytokine synthesis or proliferation (DM Essayan, Biochem Pharmacol 57: 965-973, 1999). Substances which inhibit the secretion of the afore-mentioned proinflammatory mediators are those which inhibit PDE4. PDE4 inhibition by the compounds according to the invention is thus a central indicator for the suppression of inflammatory processes.

Methods for measuring inhibition of PDE4 activity

The PDE4B2 (GB no. M97515) was a gift of Prof. M. Conti (Stanford University, USA). It was amplified from the original plasmid (pCMV5) via PCR with primers Rb9 (5'- GCCAGCGTGCAAATAATGAAGG -3') and Rb10 (5'- AGAGGGGGATTATGTATCCAC -3') and cloned into the pCR-Bac vector (Invitrogen, Groningen, NL).

The recombinant baculovirus was prepared by means of homologous recombination in SF9 insect cells. The expression plasmid was cotransfected with Bac-N-Blue (Invitrogen, Groningen, NL) or Baculo-Gold DNA (Pharmingen, Hamburg) using a standard protocol (Pharmingen, Hamburg). Wt virus-free recombinant virus supernatant was selected using plaque assay methods. After that, high-titre virus supernatant was prepared by amplifying 3 times. PDE was expressed in SF21 cells by infecting 2×10^6 cells/ml with an MOI (multiplicity of infection) between 1 and 10 in serum-free SF900 medium (Life Technologies, Pais-

ley, UK). The cells were cultured at 28°C for 48 – 72 hours, after which they were pelleted for 5-10 min at 1000 g and 4°C.

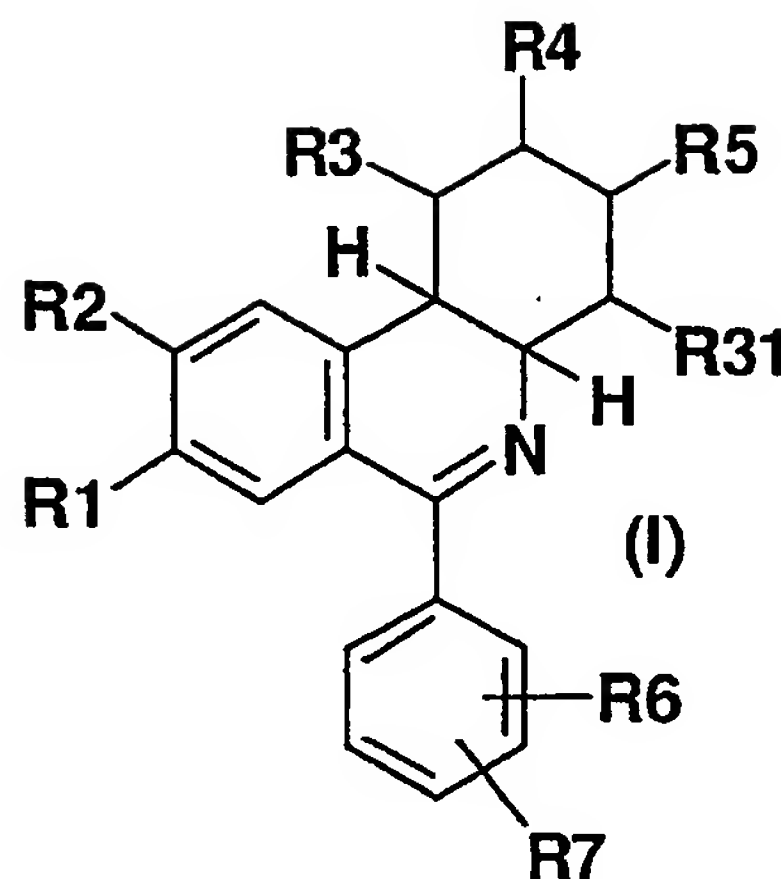
The SF21 insect cells were resuspended, at a concentration of approx. 10^7 cells/ml, in ice-cold (4°C) homogenization buffer (20 mM Tris, pH 8.2, containing the following additions: 140 mM NaCl, 3.8 mM KCl, 1 mM EGTA, 1 mM $MgCl_2$, 10 mM β -mercaptoethanol, 2 mM benzamidine, 0.4 mM Pefablock, 10 μ M leupeptin, 10 μ M pepstatin A, 5 μ M trypsin inhibitor) and disrupted by ultrasonication. The homogenate was then centrifuged for 10 min at 1000xg and the supernatant was stored at -80°C until subsequent use (see below). The protein content was determined by the Bradford method (BioRad, Munich) using BSA as the standard.

PDE4B2 activity is inhibited by the said compounds in a modified SPA (scintillation proximity assay) test, supplied by Amersham Biosciences (see procedural instructions "phosphodiesterase [3H]cAMP SPA enzyme assay, code TRKQ 7090"), carried out in 96-well microtitre plates (MTP's). The test volume is 100 μ l and contains 20 mM Tris buffer (pH 7.4), 0.1 mg of BSA (bovine serum albumin)/ml, 5 mM Mg^{2+} , 0.5 μ M cAMP (including about 50,000 cpm of [3H]cAMP), 1 μ l of the respective substance dilution in DMSO and sufficient recombinant PDE (1000xg supernatant, see above) to ensure that 10-20% of the cAMP is converted under the said experimental conditions. The final concentration of DMSO in the assay (1 % v/v) does not substantially affect the activity of the PDE investigated. After a preincubation of 5 min at 37°C, the reaction is started by adding the substrate (cAMP) and the assay is incubated for a further 15 min; after that, it is stopped by adding SPA beads (50 μ l). In accordance with the manufacturer's instructions, the SPA beads had previously been resuspended in water, but were then diluted 1:3 (v/v) in water; the diluted solution also contains 3 mM IBMX to ensure a complete PDE activity stop. After the beads have been sedimented (> 30 min), the MTP's are analyzed in commercially available luminescence detection devices. The corresponding IC_{50} values of the compounds for the inhibition of PDE activity are determined from the concentration-effect curves by means of non-linear regression.

Representative inhibitory values determined for the compounds according to the invention follow from the following table A, in which the numbers of the compounds correspond to the numbers of the Examples.

Table A: Inhibition of the PDE4 activity

| Compound | $-\log IC_{50}$ (mol/l) |
|----------|-------------------------|
| 1 | 9.15 |
| 3 | 8.74 |

Patent Claims**1. Compounds of formula I**

in which

either, in a first aspect (aspect 1) according to the present invention,

R1 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-4C-alkoxy, and

R2 is 2,2-difluoroethoxy,

or, in a second aspect (aspect 2) according to the present invention,

R1 is 2,2-difluoroethoxy, and

R2 is hydroxyl, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R3 is hydrogen or 1-4C-alkyl,

R31 is hydrogen or 1-4C-alkyl,

either, in a first embodiment (embodiment a) according to the present invention,

R4 is -O-R41, in which

R41 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-7C-alkylcarbonyl, or completely or predominantly fluorine-substituted 1-4C-alkyl, and

R5 is hydrogen or 1-4C-alkyl,

or, in a second embodiment (embodiment b) according to the present invention,

R4 is hydrogen or 1-4C-alkyl, and

R5 is -O-R51, in which

R51 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-7C-alkylcarbonyl, or completely or predominantly fluorine-substituted 1-4C-alkyl,

R6 is hydrogen, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, halogen, nitro, cyano, hydroxyl, 1-4C-alkylcarbonyloxy, amino, mono- or di-1-4C-alkylamino, phenyl, phenyl-1-4C-alkyl, 1-4C-alkyl-carbonylamino, phenoxy, 1-4C-alkylcarbonyl, or C(O)OR₆₁, wherein

R₆₁ is hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl,

R7 is hydrogen, 1-4C-alkyl, hydroxyl, halogen, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy or C(O)OR₆₁,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

2. Compounds of formula I according to claim 1 in which

either, in a first aspect (aspect 1) according to the present invention,

R1 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy, and

R2 is 2,2-difluoroethoxy,

or, in a second aspect (aspect 2) according to the present invention,

R1 is 2,2-difluoroethoxy, and

R2 is 1-2C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R₃₁ is hydrogen,

either, in a first embodiment (embodiment a) according to the present invention,

R4 is -O-R₄₁, in which

R₄₁ is hydrogen or 1-4C-alkylcarbonyl, and

R5 is hydrogen,

or, in a second embodiment (embodiment b) according to the present invention,

R4 is hydrogen, and

R5 is -O-R₅₁, in which

R₅₁ is hydrogen or 1-4C-alkylcarbonyl,

R6 is 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 3-7C-cycloalkylmethoxy, halogen, nitro, cyano, hydroxyl, 1-4C-alkylcarbonyloxy, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, phenoxy or C(O)OR₆₁, wherein

R₆₁ is hydrogen or 1-4C-alkyl,

R7 is hydrogen, halogen, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, or 3-7C-cycloalkylmethoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

3. Compounds of formula I according to claim 1 in which

- 40 -

either, in a first aspect (aspect 1) according to the present invention,

R1 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,
and

R2 is 2,2-difluoroethoxy,

or, in a second aspect (aspect 2) according to the present invention,

R1 is 2,2-difluoroethoxy, and

R2 is 1-2C-alkoxy, 2,2-difluoroethoxy, or completely or predominantly fluorine-substituted 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is -O-R41, in which

R41 is hydrogen or 1-4C-alkylcarbonyl,

R5 is hydrogen,

R6 is 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy, 3-7C-cycloalkylmethoxy, halogen, nitro, cyano, hydroxyl, 1-4C-alkylcarbonyloxy, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, phenoxy or C(O)OR61, wherein

R61 is hydrogen or 1-4C-alkyl,

R7 is hydrogen, halogen, 1-4C-alkoxy, completely or predominantly fluorine-substituted 1-4C-alkoxy,
or 3-7C-cycloalkylmethoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

4. Compounds of formula I according to claim 1 in which

either, in a first aspect (aspect 1) according to the present invention,

R1 is 1-2C-alkoxy, and

R2 is 2,2-difluoroethoxy,

or, in a second aspect (aspect 2) according to the present invention,

R1 is 2,2-difluoroethoxy, and

R2 is 1-2C-alkoxy,

R3 is hydrogen,

R31 is hydrogen,

R4 is -O-R41, in which

R41 is hydrogen,

R5 is hydrogen,

R6 is halogen

R7 is hydrogen,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

5. Compounds of formula I according to any of the preceding claims in which

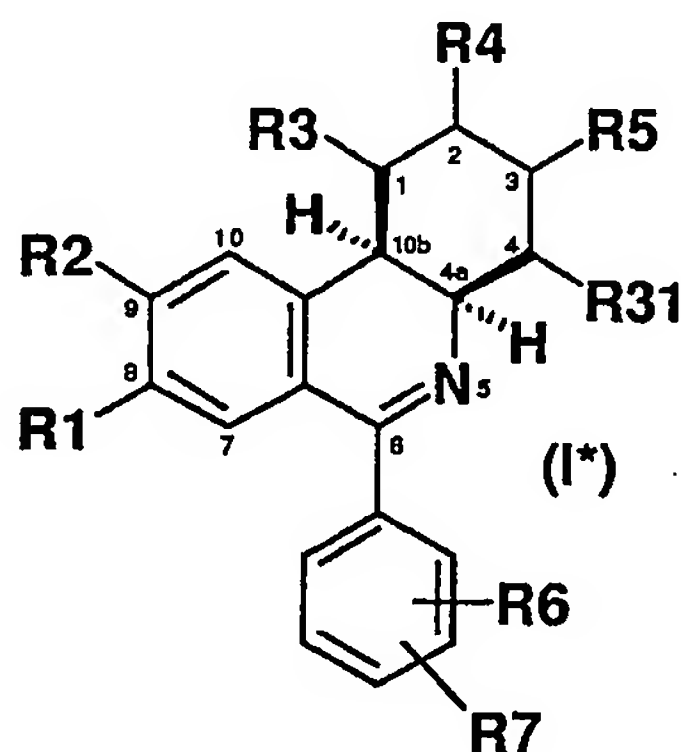
R1 is 1-2C-alkoxy, such as e.g. methoxy, and
 R2 is 2,2-difluoroethoxy,
 and the salts, the N-oxides and the salts of the N-oxides of these compounds.

6. Compounds of formula I according to claim 1 in which

R1 is 1-2C-alkoxy,
 R2 is 2,2-difluoroethoxy,
 R3 is hydrogen,
 R31 is hydrogen,
 R4 is -O-R41, in which
 R41 is hydrogen,
 R5 is hydrogen,
 R6 is cyano, or halogen such as e.g. fluorine,
 R7 is hydrogen,

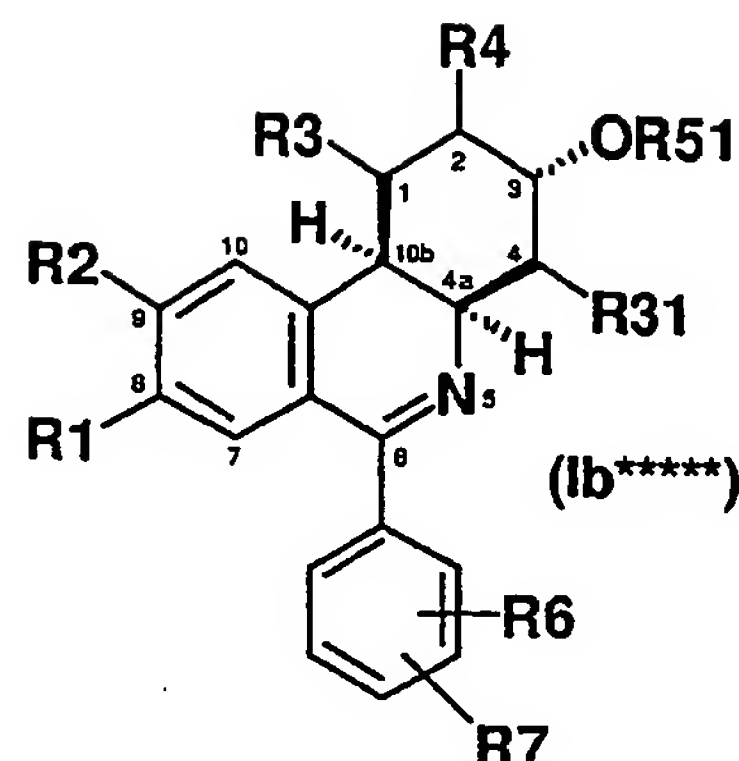
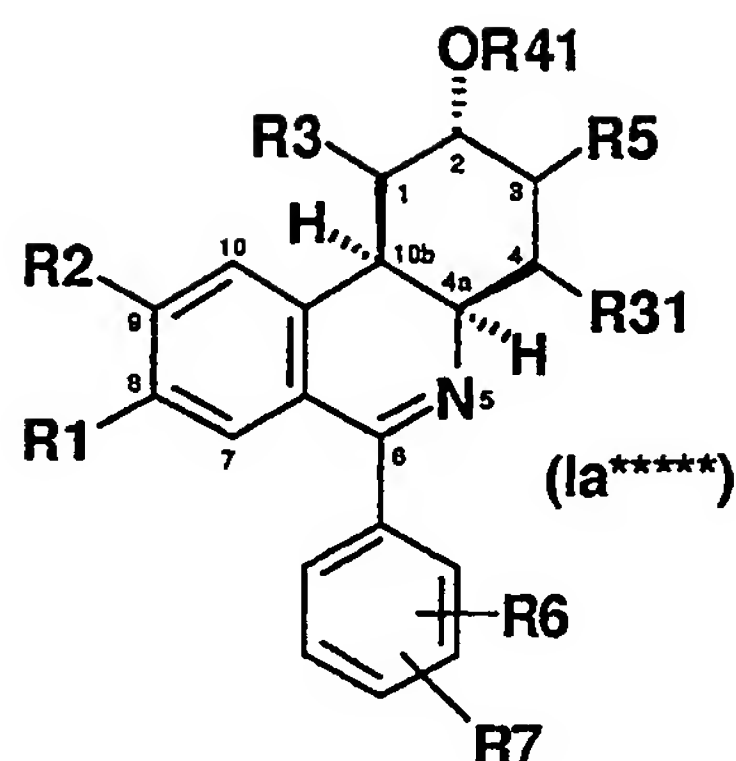
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

7. Compounds of formula I according to any of the preceding claims, which have with respect to the positions 4a and 10b the configuration shown in formula I*:



and the salts, the N-oxides and the salts of the N-oxides of these compounds.

8. Compounds of formula I according to any of the preceding claims, which have with respect to the positions 2, 4a and 10b the configuration shown in formula Ia*****, or, which have with respect to the positions 3, 4a and 10b the configuration shown in formula Ib*****:



and the salts, the N-oxides and the salts of the N-oxides of these compounds.

9. Compounds of formula I as claimed in claim 1 for use in the treatment of diseases.
10. A pharmaceutical composition comprising one or more compounds of formula I as claimed in claim 1 together with customary pharmaceutical excipients and/or vehicles.
11. The use of compounds of formula I as claimed in claim 1 for the production of pharmaceutical compositions for treating respiratory disorders.
12. The use of compounds of formula I as claimed in claim 1 for the production of pharmaceutical compositions for treating PDE-mediated disorders.
13. A method for treating illnesses in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula I as claimed in claim 1.
14. A method for treating airway disorders in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula I as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2005/051022

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D221/12 A61K31/473

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | WO 97/35854 A (BYK GULDEN LOMBERG CHEM FAB ; GUTTERER BEATE (DE)) 2 October 1997 (1997-10-02) cited in the application page 44 - page 45; claim 1 | 6 |
| A | ----- | 1-5, 7-14 |
| P, Y | WO 2004/019944 A (SCHMIDT BEATE ; KAUTZ ULRICH (DE); ALTANA PHARMA AG (DE)) 11 March 2004 (2004-03-11) cited in the application page 63; claim 1 page 38; example 52 | 6 |
| P, A | the whole document | 1-5, 7-14 |
| P, A | ----- WO 2004/019945 A (SCHMIDT BEATE ; KAUTZ ULRICH (DE); ALTANA PHARMA AG (DE)) 11 March 2004 (2004-03-11) the whole document ----- | 1-14 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

11 August 2005

Date of mailing of the international search report

19/08/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/051022

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13 and 14 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP2005/051022

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9735854 | A | 02-10-1997 | DE 19613091 A1 | 09-10-1997 |
| | | | AT 224386 T | 15-10-2002 |
| | | | AU 718752 B2 | 20-04-2000 |
| | | | AU 2291097 A | 17-10-1997 |
| | | | CA 2250569 A1 | 02-10-1997 |
| | | | CY 2431 A | 12-11-2004 |
| | | | DE 59708265 D1 | 24-10-2002 |
| | | | DK 889886 T3 | 20-01-2003 |
| | | | WO 9735854 A1 | 02-10-1997 |
| | | | EP 0889886 A1 | 13-01-1999 |
| | | | ES 2184077 T3 | 01-04-2003 |
| | | | JP 2000507256 T | 13-06-2000 |
| | | | PT 889886 T | 28-02-2003 |
| | | | SI 889886 T1 | 28-02-2003 |
| | | | US 6127378 A | 03-10-2000 |
| WO 2004019944 | A | 11-03-2004 | AU 2003255493 A1 | 19-03-2004 |
| | | | CA 2495827 A1 | 11-03-2004 |
| | | | WO 2004019944 A1 | 11-03-2004 |
| | | | EP 1539164 A1 | 15-06-2005 |
| WO 2004019945 | A | 11-03-2004 | AU 2003273805 A1 | 19-03-2004 |
| | | | CA 2496459 A1 | 11-03-2004 |
| | | | WO 2004019945 A1 | 11-03-2004 |
| | | | EP 1536798 A1 | 08-06-2005 |